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Section of Physical Medicine

President—W. YEOMAN, M.D.

[*February* 14, 1951]

DISCUSSION: THE MECHANISM OF PAIN AND ITS RELIEF BY PHYSIOTHERAPEUTIC MEASURES

Dr. J. H. Kellgren: When proposing to relieve pain by physical measures it is well to remember that this distressing symptom is not just an unpleasant sensation, but rather an elaborate and varying symptom complex with many components both sensory, emotional and reflex. Thus every patient complaining of pain presents a separate problem, and success in therapy depends upon a correct assessment of the individual case.

We must first decide whether our patient is in fact suffering from an abnormal sensation of pain, for there are many who merely react abnormally to sensations which in themselves are not remarkable. We all have our weak spots, whether it be in the back, the feet or elsewhere, and we most of us suffer from aches and pains from time to time but we recognize these sensations for what they are, the aches and pains of everyday life and we disregard them; but there are some people to whom these everyday pains appear as distressing and disabling symptoms requiring treatment. Such people may be said to have a low reaction threshold to pain, a very real disability.

Patients with such a low reaction threshold often derive some benefit from physiotherapy, particularly if the treatment is elaborate and impressive and produces a feeling that something is being done. Yet this benefit is often shortlived and if one is too successful in curing the old pain they frequently return with a new one in some other part of the body and so become chronic haunters of treatment clinics.

Then there are those in whom mental tension expresses itself as widespread muscular tension. They move stiffly and awkwardly, contracting agonists and antagonists simultaneously. This muscular inefficiency leads to fatigue and painful muscle strains. These patients provide a typical example of the psychosomatic mechanism. There is also the completely psychogenic pain, in which the patient has projected his emotional anguish into some convenient part of the body where he keeps it quite cheerfully as an "agonizing pain". These pains are bizarre in distribution, constant in intensity, and completely unaffected by any form of therapy, and indeed we are probably doing the patient a disservice in attempting to undo his solution of his agonizing problem.

In all these conditions the mechanism primarily responsible for the complaint of pain is not located in the part complained of; and it is doubtful whether treating the part locally by physical or other measures is really a wise procedure.

If, on the other hand, we decide that our patient is suffering from a genuine painful sensation of abnormal intensity we are on much surer ground. Here it is useful to think of the cause of pain in terms of disorders of the pain nerves themselves, and disorders of the surrounding tissues. The latter are the most common, being the cause of the pain that accompanies trauma, infection and rheumatic disease. In these conditions there are probably physiochemical changes in the damaged tissues which may stimulate the pain nerves directly causing spontaneous pain. Alternatively these physiochemical changes may render the pain nerves more sensitive to mechanical, thermal and other stimuli, so producing pain on movement, pain on cooling and warming, tenderness to pressure and so on.

These chemical pain mechanisms tend to be in a state of delicate equilibrium and they are greatly affected by the state of the local blood flow, since the circulating blood tends to remove or destroy the pain-producing substances.

This state of balance can be shown up by applying short periods of arterial occlusion and venous congestion to a limb affected by trauma, infection, or other pain-producing lesions (Fig. 1). In many instances occlusion of only a few minutes' duration produces the most dramatic increase of pain, causing the subject to become pale, sweating and acutely distressed. Venous congestion produces some increase of pain in many instances but this is usually only of a slight degree and is not progressive, and in these cases it is probable that tissue tension plays some part in the production of pain. A considerable variety of painful lesions has been studied by such simple tests (Addis, Jepson and Kellgren, 1950) and the results are shown in Table I.

The table shows the number of cases of each type of pathological lesion in which arterial occlusion or venous congestion produced either no change, a slight increase of pain or a severe increase of pain, necessitating release of the cuff before the elapse of ten minutes. In 13 of these cases venous congestion was omitted.

It will be seen that acute closed infections are most dramatically affected by alteration of the circulation, and that traumatic lesions, such as wounds, fractures, sprains and strains are also considerably affected by the tests and had more of the traumatic lesions been severe and acute I think the results would have been very similar to those in the infective group.

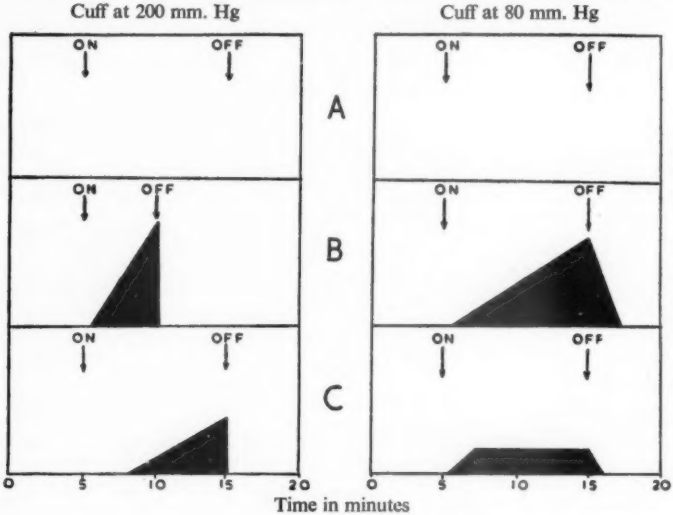

FIG. 1 illustrates the three types of response to short periods of arterial occlusion and venous congestion. A, No effect. B, Rapid increase of pain. C, Slight or modified increase of pain. The black areas represent spontaneous pain. (Fig. 1 and Table I are reproduced from *Clin. Sci.*, 1950, **9**, 272 and 274 by permission.)

TABLE I

Type of lesion	Pain from occlusion			Pain from congestion		
	Severe	Slight	None	Severe	Slight	None
Closed deep suppuration ..	18	7		1	8	7*
Operation wounds	6	4		1	8	1
Minor fractures and sprains ..	1	9	10	1	8	10
Superficial suppuration ..		9	10		5	11
Rheumatoid arthritis		11	14		11	14
Heberden's nodes		3	3		3	3
Osteoarthritis		1	4		1	4
Tuberculous arthritis			4			4
Ankylosing spondylitis ..			3			3
Nerve injury. Type I			10			10
Nerve injury. Type II ..			10			10
Glomus tumour			5			5
Miscellaneous	2		7		1	8
Totals	27	44	80	3	45	90

* In 3 of these painful throbbing was relieved by venous congestion.

The rheumatoid lesions were only slightly affected, although many acutely inflamed joints were tested. This may be because in this condition the physiochemical changes involve primarily the macromolecular connective tissue substances such as collagen and the polysaccharides which do not readily pass in and out of the blood. The acute painful episodes which sometimes accompany osteoarthritis are greatly affected by changes in blood flow but as one would expect osteoarthritic lesions are generally unaffected. Among the arthritic lesions tuberculosis and ankylosing spondylitis also remain unaffected. The nerve injuries and glomus tumours are examples of lesions in which there are changes in the pain nerves themselves often of an anatomical nature. It is therefore not surprising that in these the pain remains completely unaffected by changes in the circulation.

The state of the local circulation is therefore of paramount importance in traumatic and acute inflammatory lesions and it is just in these conditions that physiotherapy is so successful in relieving pain. From the studies of Barcroft and Edholm (1943) we know that forearm blood flow which is thought to be mainly muscular may be reduced to a very low level by cooling the part and conversely it can be greatly increased by warming. Dr. Janus, in my laboratory, has been making similar plethysmographic studies of knee blood flow which is mainly articular and a typical study is shown in Fig. 2. From this it is clear that a rise in knee temperature of only 5° C. will cause a threefold increase in blood flow.

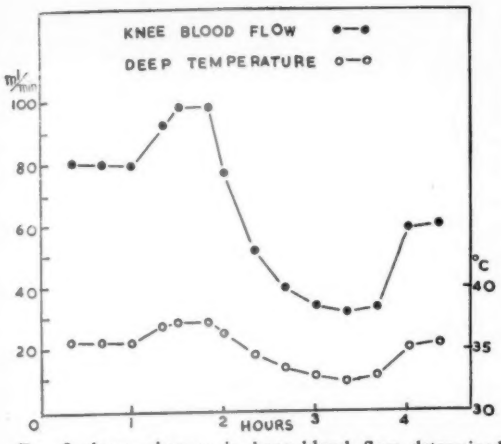

FIG. 2 shows changes in knee blood flow determined plethysmographically, in relation to alterations in knee temperature recorded by a thermocouple lying deep to the patellar tendon.

In our raw climate the temperature inside the muscles and joints is usually well below 37° C. and in the extremities it not infrequently falls below 30° C., when blood flow becomes very low indeed. A great increase in blood flow may therefore result from warming the part, and in those painful conditions which are affected by changes in blood flow a corresponding relief of pain is to be expected.

Although the painful nerve injuries we studied remained unaffected by alterations in blood flow, in some cases pain could be induced by cooling the part and relieved by warming it again. This occurred equally if warming and cooling was done during a period of arterial occlusion so that it is clear that temperature changes in these cases affected pain directly, and not as a result of changes in local blood flow. In this direct way temperature changes affect deep and cutaneous pain quite differently so that for this purpose these two types of pain must be considered separately.

If the normal deep tissues are cooled rapidly deep pain is experienced while the temperature of the tissues is falling from 30° to 15° C., but as cooling proceeds analgesia develops and becomes complete when the tissue temperature reaches about 10° C.; but if the tissues are cooled slowly analgesia develops without appreciable pain and this is what happens under normal conditions of exposure. If on the other hand the deep tissues are abnormally sensitive as a result of trauma or disease pain may result from even very slow cooling and analgesia fails to develop normally so that the pain persists until the part is warmed up again (Kellgren, McGowan and Hughes, 1948). This mechanism of cold pain is found in most conditions in which there is hyperalgesia of the deep tissues, and since it is often accompanied by muscle spasm and vasospasm a thorough warming may give more than temporary relief and provides a valuable period of comfort, during which the function of the painful disused part may be restored.

The effect of temperature on cutaneous pain was studied extensively by Lewis (1942). In normal skin pain results from heating above 43° C. or cooling below 10° C., but in the erythralgic state cutaneous pain may result from temperatures as low as 30° or as high as 15° C. Thus in these lesions warmth causes an increase of pain, and cooling between 30° and 15° C. gives relief. Increased pain from warmth is also found in impending gangrene and other conditions in which the arteries are blocked and unable to allow the normal increase of blood flow in response to warming.

Cutaneous and deep sensations differ in other respects, thus cutaneous pain takes precedence over deep pain in consciousness and this fact may be used to mask certain tiresome deep pains of low intensity. Suitable cutaneous sensations can be produced by a mild ultraviolet burn, the Kromeyer patch being a typical example. These patches are most useful in relieving continuous spontaneous deep pains of low intensity, but they are of little value in controlling the sudden severe pains such as result from movement of a tender joint. Most physiotherapy should be directed at the diseased structure from which the symptoms are arising but if we are aiming at masking a deep pain the cutaneous patches should be placed over the part to which pain is referred irrespective of its source.

Physiotherapy may also relieve pain *indirectly* by preventing the development of painful states. Thus, by regaining full motion in stiff joints, recurrent painful sprains of these joints are prevented. Similarly weakened and wasted muscles and muscles in poor training are very liable to recurrent painful strains, which can be avoided by suitable muscle training. Where deformity or other mechanical defects such as torn ligaments are a source of recurrent painful sprains and strains intensive muscle training may be able to overcome the mechanical defect and again pain may be relieved by prevention. Indeed this indirect method of relieving pain is probably one of the most valuable fields of therapy in which physical means are absolutely indispensable.

A complaint of pain may result from disorders at three different levels in the human organism: (1) From disorders of the body tissues such as are commonly found in trauma, infections or rheumatic disease. In these conditions chemical mechanisms are prominent, and much relief may be obtained by the correct use of physiotherapy. (2) Disorders of the pain receptors and pathways in the nervous system such as occur in painful nerve injuries and neuropathies. The cause of pain in these conditions is as yet poorly understood, and it is less easily relieved, perhaps because in our ignorance of the mechanism by which it is produced we are unable to apply the right kind of physiotherapy for each individual case. (3) Finally, a complaint of pain may result from an abnormal emotional, intellectual or reflex reaction to a painful sensation which is not in itself remarkable, or it may result from gross psychiatric disturbances. In these cases it may be unwise to treat the part complained of because it is not, in fact, the seat of the causative disorder.

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Dr. Clive Shields: The definition of "pain" defies the efforts of poets, lexicographers and scientists. Sherrington's (1906) "psychical adjunct of an imperative protective reflex" fails at the clinical level. The ancients wrote little of pain until about 320 B.C. when Aristotle described it as "a passion of the soul".

The differentiation of touch and pain end-organs was first demonstrated by Schiff in 1858 and confirmed by many workers since. In 1941 Sir Thomas Lewis (1942) suggested that some histamine-like body, possibly acetylcholine, was concerned in the pain mechanism. Wolff and his co-workers (1948) in America were able by laboratory methods to differentiate between the *perception* of pain and the *reaction* to pain, and they devised a unit of pain which they called the "dol".

Adrian (1950) in a recent paper wrote, " . . . pain signals themselves play little part in the elaboration of cortical and mental patterns", and elaborated this in a private communication thus, "it is the thoughts associated with pain, e.g. fear of death, anxiety, disappointment, which start the cortex building up and elaborating these thoughts and thus gradually creating the individual's general concept of the experience".

Whereas with all the other senses, disuse to some extent blunts their acuity, pain alone needs no practice to maintain its potency. "Conditioning" may, however, mitigate its effect.

Pre-frontal leucotomy performed for intractable pain affords some support for the idea of differentiation between perception and reaction, and such cases are able to cease analgesic drugs without exhibiting the usual "withdrawal syndrome". The fact that injection or ionization of histamine causes, not pain, but *itch*, gives rise to the suggestion that in the pain mechanism the intermediate substance is a specific cell-enzyme, activated or inactivated by its environment; since such a body would act merely as a catalyst the explanation of non-fatigability in pain end-organs may be found.

Physical measures which relieve pain do so either by suggestion (directed to the reaction component), by "counter-irritation" (which prevents spatial summation from operating) or, where the direct current is used, by inactivating the hypothetical cell-enzyme. Heat, by increasing the local circulation, reduces the concentration of the intermediate substance. When rest is effective it operates by reducing frictional irritation in muscles, tendons and peri-articular structures.

Modified exercise may relieve pain in peripheral circulatory failure by improving the collateral circulation.

Wolff's (1947) lately re-enunciated theory of internuncial neurones in the dorsal horn, first put forward by Sturge in 1883, in conjunction with a specific cell-enzyme, might explain many problems in connexion with the pain mechanism, more particularly areas of hyperalgesia remote from injured tissue, "phantom" limb pain, and some anomalies of referred pain which cannot be explained on a purely segmental basis.

This essay is to be published *in extenso* elsewhere.

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Section of Pathology

President—Professor WILSON SMITH, M.D., F.R.S.

[*March* 20, 1951]

SYMPOSIUM: THE PLACE OF PATHOLOGY IN UNDERGRADUATE MEDICAL EDUCATION

Professor W. G. Barnard: In my view the place of pathology in medical education is in the clinical period and throughout it. It should form one of the essential parts of the Final qualifying examination.

PATHOLOGY

By pathology I mean the study of disease processes, their cause, development, progress and termination, and also how the body reacts to disease and the means by which it manages to evade or compensate for abnormalities resulting from disease or injury. Thus bacteriology, biochemistry, morbid anatomy and histology and various experimental techniques all contribute to this many-sided science. It is important to emphasize that pathology is a science, that it has earned for itself a place among the sciences, that it is worthy of study for its own sake and that it has its own outlook which differs from the medical outlook. Because of its growth, it must be clear that it is impossible to teach the whole to an undergraduate student. The only parts that should be taught are the general principles which have stood the test of time and criticism. Just as I believe it is wrong to attempt to teach the histological appearance of all tumours, so I consider it wrong to attempt to teach the characteristics of all bacteria. There are, however, fundamental facts which might be described as laws of tumour formation and these should be taught, just as the laws of immunity and immunological reactions should be taught. Should we be successful in teaching a student the general principles of pathology he will himself be able to appreciate any form of special pathology which comes to his notice. By a knowledge of general principles he will have acquired a foundation on which to build. Without such general principles his knowledge may be vast but because of the missing links it will be unco-ordinated.

FUNCTION AND STRUCTURE

Living form is inseparably connected with matter, that is with structure. As pathologists we have tended to interest ourselves too much with the structure and not enough with activity or function. So long as the form is living, so long will it exhibit activity and this will be measured by biochemical and physical means. For this reason the still waters of pathology in recent times have been erupted by the incursion if not invasion of biochemists and we must expect and welcome a similar contribution from biophysicists. The laws governing all these actions and reactions are biological, chemical or physical laws. Just so long as the animal is in a condition that is within the limits of normal it is in a physiological condition. When the condition is outside these limits it becomes pathological. In the past, because illness was regarded as unnatural or supernatural, pathological processes were also regarded as unnatural in the sense of being outside or beyond nature. This fallacy has crept

into pathology, the truth of course being that the biological laws hold and the pathological state is one in which they operate in unusual or abnormal conditions. It is the conditions which have changed not the laws.

Since the normal laws of reaction of living tissues are the province of biology and, as far as man is concerned, that of physiology, it is essential that pathology and human physiology should be closely linked.

Pre-clinical Course

In London the student for his Second Examination is expected to learn the whole of anatomy, physiology, biochemistry and some pharmacology in five academic terms or a little less. This makes it impossible to introduce anything else into this period. At Oxford and Cambridge the students are more fortunate. They have a three-year course and for all practical purposes they are not admitted until they have gained their 1st M.B. With such an extended time it is possible to introduce pathology into the pre-clinical period. As far as the students are concerned this is immensely popular and it does introduce them to pathology. It is of the first importance to appreciate that even here the teaching is done entirely by pathologists. Until recently they were a little handicapped by the absence of clinical material, but even so this preliminary instruction was of value. In London, for the reason I have given, it would be impossible to introduce any such course before the clinical period.

Introductory Clinical Course

For many years now in some medical schools there has been an introductory period between the pre-clinical and the clinical course proper. This elementary or preliminary clinical course has now become almost universal. I have heard no serious criticisms of it in recent times. There is, however, disagreement as to its length and its content. We believe at St. Thomas's Hospital that anything less than six months is too short and that an appreciable proportion of the time should be devoted to pathology. During the first three months of this period the students spend four afternoons a week at lecture demonstrations and have two 9 o'clock lectures a week. During this time they are taught the principles of general pathology including bacteriology, chemical pathology, and clinical pathology. In their practicals they carry out tests illustrating these principles and examine histological and other preparations.

I believe that instruction in pathology should be continued throughout the clinical period. With us this is done in the following ways: By attendance in the post-mortem room, where brief demonstrations and discussions take place between 1.30 and 2 p.m. every day. This time is chosen because it is easy for the clinicians to be present and also for the majority of students to attend. Most "firms" have a weekly clinico-pathological conference at which the students present the case, the clinical story and the pathological findings and both a clinician and a pathologist are present to assist, to answer questions, or to point out any lessons that have emerged. There is also a monthly clinico-pathological conference at which a clinician from some other hospital or even another country is the principal speaker. During the final year there is an advanced course in pathology consisting of two half-days a week for three months. Students in their final year are also allowed to act as clerks in the Department of Pathology for a month. This is purely voluntary and consequently most students want to do it.

Throughout the medical curriculum there must be an overlap between the various subjects. Experience has shown that this overlap must be from above downwards. Physiologists should not attempt to teach pathology; neither should biologists attempt to teach physiology. In spite of this I believe that there is room for a closer

liaison between physiology and pathology and with a close liaison pathology could contribute materially to the easy passage of the student from physiology to medicine.

Medical Education

As a Dean, I should say something about medical education in its wider aspects. What are we trying to do? I can only answer for myself and the School I have the honour to serve. We are trying to give a medical education that will serve as a basis on which the general practitioner and practitioners of all other branches of medicine can build. The most recent description of the kind of practitioner was given by J. T. Christie, Master of Jesus College, Oxford; this is what he said:

> "He was not, I think, a very clever man, that doctor, and always ready to co-operate with the expert. He loved life in himself, and in others, and was specially fond of youth for that reason. He fought against death with open eyes, and he hated shams. Only the shams disliked him. He was a strong Radical by tradition and conviction, and, long before it was the fashion, championed the claims of the village boys to have their own sports field. He brought me and my brother into the world; took us shooting, included us in the village cricket sides, beat us good-naturedly at tennis, and never minded losing, though he rarely lost. He had domestic sorrows of his own, but he was always cheerful, though never 'cheery', and never patronizing. In a little community, where the parson's influence was waning every year, he was much more than a doctor to the village: he was its councillor and friend. He died not long ago, wholly unaware, I believe, of all that he had done, because he did it unconsciously."

Because this is our aim, we put character before scholastic level in selecting our students. We believe they must have a grounding in chemistry, physics and biology. We do not mind these subjects being related to possible medical aspects, although we do not believe they should be too closely limited. The students must have a sound basis of human physiology and biochemistry and a good working knowledge of human anatomy.

The difficulty in the clinical period is to effect a balance between the competing claims of medicine, surgery, obstetrics, gynæcology, pathology and all the specialties. We believe that most of the students' time in the clinical period should be spent with patients and they must be guarded from too much instruction.

Professor L. P. Garrod: There is a tendency to regard pathology merely as a diagnostic aid, and to require that students be taught no more than the rudiments of its practical use for this purpose. I feel that in a meeting of this Section we must affirm that pathology in all its branches is the scientific foundation of the whole of medicine, and that a sound knowledge of its principles as well as its commoner techniques is essential for intelligent clinical practice. This claim entitles us to a substantial share of the student's time for our teaching. On the other hand, the curriculum is becoming steadily more crowded, and unless it is to be lengthened we must weigh the merits of our subject against those of others. I was horrified by a recent article by my colleague, Mr. H. B. Stallard, on the teaching of ophthalmology, citing many cases in which sight was unnecessarily lost owing to the doctor's lamentable ignorance of this specialty. We cannot dispute that it is more important for the practitioner to be able to recognize and treat acute glaucoma than, for example, to understand the theory of the complement-fixation test.

We are faced with the problem not only of how much to teach but when to teach it. It is difficult to appreciate the subject without some knowledge of medicine, but the converse is equally true, and the solution is to divide the course into two parts. At St. Bartholomew's Hospital we include about eight classes in elementary general bacteriology in the "introductory course" with which the clinical period begins, and follow this with a full three months' course taken at the end of the first clinical year, which in my opinion is too early for it. This consists of forty sessions each including a lecture and practical work, and embraces not only bacteriology and immunology,

but protozoology and parasitology. It is emphatically a course in microbiology as applied to medicine: we have no time in medical schools for treating the subject as an independent science. If this is to be done, it must come into biology in the first pre-clinical year, and I suggest that the replacement by bacteriology of some of the botany now taught is a possibility worthy of discussion.

Three aspects of the subject call for special emphasis in our main course of instruction. The first is how infection is acquired, and here I think we should define our respective spheres with those whose duty it is to teach Public Health. In as far as they are willing to hand over to the bacteriologist the subjects of the hygiene of water, milk and other foods and the transmission of infection by air and dust and from animals, I think these may be dealt with better in a course on bacteriology. The second is laboratory diagnosis. Even those with the lowest view of our subject admit that it is useful to a doctor to know what tests will assist him in diagnosis and how to interpret their results. He should also know how they are done, if only that he may furnish suitable specimens and have some idea of how long he may reasonably be expected to wait for an answer.

The third aspect is the treatment or prevention of infection by specific means. It is emphatically our duty to teach the principles of immunology and the practice of immunization in its commoner aspects. In this country particularly, where so many people object to inoculations on principle or because they have been deluded by the propaganda of anti-vaccinationists and objectors to vivisection, every doctor should have reasoned arguments at his command to support what he knows it is his duty to do. He should also know enough about immunization to distinguish between methods which are well founded and dependable, and those which are only in the experimental stage or frankly unsupported by any sound evidence. In the sphere of treatment we also have our part to play in connexion with chemotherapy, particularly that of bacterial infections. How we should share this subject with the pharmacologist and the clinician is a question which remains to be settled.

Our most difficult task is to provide suitable practical work. I take the view very strongly that students should be enabled to do such work themselves, and not merely be furnished with demonstrations. Moreover they should work with material containing living pathogenic organisms and not spurious substitutes. One object of this is to enable them to carry out certain simple examinations themselves in case of necessity: there are plenty of circumstances in which a pathologist will not be available and a few bottles of stain and a microscope are all that is needed to gain vital information. It is not to be expected that the average student will attain proficiency in more elaborate techniques, but it is well worth while for him to practise them. The secret of their usefulness is this; that the student takes far more interest in films and cultures he has made himself, however bad they are, than in anything he is merely shown, however perfect. He will remember what he has done, even though he forgets what he is told.

Practical exercises which we never omit are swabbing the nose and post-nasal space and the performance of Schick tests. Students carry out these operations on one another and do them surprisingly well. I should like to include smallpox vaccination as a practical exercise in connexion with virus diseases, but this is unfortunately still catered for in a separate and superfluous course.

The teaching of microbiology could be greatly improved by the extended use of cinematography. This is the ideal way of imparting a knowledge of manual technique, and it serves also to show the student living things which he cannot usually be enabled to examine directly. Two such films have been made in my department which we regularly show to classes: they illustrate the movements of *Entamœba histolytica* in fæces and of *Microfilaria bancrofti* in blood.

(The speaker concluded his remarks by presenting these films.)

Professor **Clifford Wilson:** If there is any controversy between clinicians and pathologists over the place of pathology in the medical curriculum it concerns only the amount and distribution of the teaching. Most of us have grown up in the tradition that a knowledge of pathology is not only important to the clinician but that it is the basis for sound medical practice. For some strange reason this view has in certain quarters become less fashionable to-day, but I feel it is largely a matter of definition. Pathology is still our basic discipline, but it has broadened tremendously in scope and significance. Twenty years ago pathology was, in the student's mind at any rate, synonymous with morbid anatomy. Bacteriology, chemical and clinical pathology played a minor role. Now the latter have advanced and expanded with the growing interest in epidemiology, antibacterial therapy, metabolic disorders and hæmatology. Furthermore a group of intruders has appeared in the form of psychopathology, social pathology and functional pathology. These intangibles are, however, symptomatic of the universal change in methods of thought and enquiry which in other spheres and other countries has produced even more dangerous doctrines. The need for a more dynamic method in teaching medicine was emphasized in a memorable article by Sir Thomas Lewis shortly before his death. He pleaded for a more deliberate and planned instruction in the processes of disease as distinct from the empirical or vocational teaching of the manifestations of disease in the individual. Other bodies and committees subsequently studying the reform of medical education have stressed the need for the teaching of principles rather than the amassing of factual knowledge. When we look into the substance of these recommendations they resolve themselves into the enlightened teaching of pathology in its fullest sense. I think the practical aspects of this teaching can best be appreciated in terms of the need for integration with the clinician, the patient and the student.

(1) *Integration with the clinician.*—There is much need and opportunity for co-operative teaching between clinicians and pathologists. Medical clerks should be taught in the Museum by means of preserved specimens illustrating their cases during their in-patient appointments. They should have group teaching in the clinical laboratories about the cases with which they are familiar. They should be encouraged to carry out themselves the simpler investigations on their own patients. The clinician and morbid anatomist should combine in the routine demonstrations in the post-mortem room. Pathologists and bacteriologists should be seen more frequently in the wards. Clinical-Pathological Conferences, although of much less educational value, can foster the spirit of co-operation between all departments. Systematic lectures in medicine, surgery and pathology should be integrated in a single course.

(2) *Integration with the patient.*—During the clinical period, pathology should be taught in much closer relation to the living patient; thus some attempt should be made to correlate disorders of structure such as cardiovascular hypertrophy and arterial degeneration with the associated disorders of function such as cardiac output and peripheral resistance. An attempt should be made to bring together all the ætiological factors in disease; for example the natural history of pulmonary tuberculosis should be dealt with in terms of morbid anatomical findings, environmental factors and the psychological reaction of the patient. The unique opportunity of teaching living pathology which surgery provides should be given greater prominence; operation specimens and microscope slides of organs removed at operation, should be brought into the ward and discussed in relation to the clinical aspects. In the teaching of morbid anatomy more attention should be paid to the ætiological and experimental aspects. Similarly in post-mortem demonstrations the cause of death should be discussed as a disorder of function and not merely as the inevitable but little understood sequel of the anatomical findings.

(3) *Integration with the student.*—It is imperative to lighten the mental burden on the medical student. Whilst we all accept the view that pathology is a scientific discipline in its own right it must always be appreciated that the majority of students are training to be clinicians and every specialist must be on his guard against the temptation of trying to teach the whole truth in his particular field. Selection in morbid anatomy, bacteriology and chemical pathology must be particularly ruthless over specialized techniques and rarities.

In planning the timing, volume and method of teaching pathology the main controversial points are:

(1) Should there be a pre-clinical as well as a clinical course?

(2) Should continuous teaching of pathology during the clinical period be supplemented by a special short course (three months) in pathology?

(3) How can the examination be modified in such a way as to make possible urgent reforms in teaching?

I am in favour of a pre-clinical course in pathology. We have an opportunity in London to contrast the approach to clinical medicine of Oxford and Cambridge students who have had pre-clinical teaching in pathology and of London students who have had none. There is no doubt that the pre-clinical course confers a great advantage. It does this by providing the student with concrete images which give meaning to abstract clinical concepts; without this preparation there is a great delay in the development of clinical understanding.

Furthermore the teaching of anatomy and physiology benefits greatly from a concurrent introduction to the abnormal. The argument has been put forward that in the London M.B. course there is no room in the pre-clinical curriculum for teaching in pathology, but room could be made and must be made by the elimination of much irrelevant and detailed matter. The pre-medical and pre-clinical subjects could be taught in a combined course over a period of two years leaving ample time for the introduction of other topics.

During the clinical period the Introductory Course should contain three or four sessions a week in pathology, which, granted a pre-clinical introduction to general pathology, can be devoted to demonstrations in special pathology closely related to the clinical teaching during this course. Continuous teaching during the clinical years should be carried out by the traditional methods of post-mortem demonstrations, Museum demonstrations (particularly by Registrars during the period of in-patient appointments), by Clinical-Pathological Conferences and by lectures or tutorial classes. I feel strongly that half-way through the clinical curriculum there should be a three-month appointment in pathology. At this stage the student will have had a fair amount of clinical experience and it is essential to consolidate the teaching in various aspects of pathology. The traditional teaching in pathology should during this course be integrated with social pathology and psychopathology. Visits to fever hospitals, sanatoria, mental hospitals, and factories should be carried out and public health and forensic medicine should be dealt with at this time. After such a course the student is enabled to proceed to special appointments in the latter half of the clinical curriculum with a more balanced approach and firmer grasp of fundamental principles.

The most important and the most difficult problem is a revision of our examination system. Changes in the examination of pathology alone will not meet the situation, since adequate reorganization of teaching in the clinical period cannot be made without changes in the pre-clinical curriculum and examinations. Until room can be found in the pre-clinical period for the teaching of pathology I do not feel that we can make any real progress with revision of the clinical half of the curriculum.

Section of General Practice

President—G. F. Abercrombie, V.R.D., M.A., M.D., K.H.P.

[*February* 28, 1951]

DISCUSSION ON THE ACUTE ABDOMEN

Dr. David Hughes: As a family practitioner I have always been very interested in the problem of acute abdomen. I cannot give an academic account of this large field, but only my views, experiences, and a few clinical observations.

For the first twelve years in practice I was single-handed, but for the last five years in a partnership of three, then four. The practice is typically rural, very scattered with several small villages, and numerous small farms dotted fairly evenly over a large area. Daily mileages of 50 and 60 are common, frequently 80, and on rare occasions I have covered even 100 miles. My own village is in the centre of the practice and the nearest hospital 9 miles away, where, until July 1948, almost all the acute surgery was done by the G.P. surgeons, for the nearest consultants were 35 miles away.

A colleague told me recently "It is not the acute abdomen that worries me, but the chronic". And although in the sense in which he meant it we can agree, it is the *urgency* that creates the worry and the anxiety in the acute case that brooks no undue procrastination or cogitation. Its challenge is immediate, and recognized by both hospital and family practitioner alike, and although in the case of the experienced consultant it may only be an interesting challenge, to the young doctor commencing practice it may appear as a threat, and failure or delay in diagnosis may have repercussions that will echo and re-echo through the practice to his detriment. I would emphasize the paramount importance of doing resident hospital appointments before entering general practice. One of these should certainly be the surgical job, because of the valuable and lasting experience it gives in dealing with the diagnosis of the acute abdomen, and for the opportunity of confirming this, and correlating the clinical signs with the exact pathology revealed at operation. I learnt more from the first few cases when the responsibility for the diagnosis in the admission ward rested on my shoulders for the first time, than all the cases I saw as a student. *Now* a firm diagnosis was necessary and *now* was the time to develop the habit of making it. In general practice the threat to life entailed in the failure to make an early diagnosis in the acute abdomen recurs more constantly than any other emergency. The way to get to know the acute abdomen is by doing a surgical job where the varying cases do not accumulate slowly as in general practice, but in rapid succession over a wide clinical field and with clinical variants in the same type of case. There are 7,200 patients in our practice and over the last five years we have sent into hospital 128 acute abdominal cases including 87 appendices of which 7 had perforated, and the remainder spread over 12 conditions, giving an incidence in the practice of 0·35% per annum. Therefore on this basis the experience of a young partner would grow but slowly and painfully with only about 6 cases a year.

In a remote rural practice there are few opportunities of calling in a consultant as second opinion. Distances and the time factor almost inevitably mean delay and this risk is unjustifiable. After my experience as a resident I resolved that if I felt a case was an acute abdomen at my first visit I would send it in to hospital immediately, and neither fields nor floods nor family nor friends should interfere, or delay the patient, once I made my diagnosis. Parents and relatives learn to trust in your opinion and advice and appreciate your readiness to take firm responsibility for your decisions. Hesitations and a reluctance to take a decision alone lead to loss of confidence. Mistakes and delayed diagnoses do occur, and have occurred with me; these I shall mention later. But generally speaking this reliance on one's own opinion does not appear to have been unduly misplaced.

The relationship between the G.P. and the surgeon is important. They should know each other socially and enjoy opportunities for discussion and so build up a healthy regard

for each other's opinion. The same surgeon should deal with the emergencies from this practitioner or practice. Close personal contact ensures that these cases will be more readily admitted as true surgical emergencies and dealt with expeditiously. There would then be less likelihood of a changing clinical picture leading to unnecessary delay in operation. Within the first month in practice I had the satisfaction of insisting on an abdomen being opened late at night for a perforated appendix in a man whose clinical picture had altered, and had I not seen him five hours previously I would not have recognized the abdomen as other than a normal one. Where the surgeon knows the practitioner to be reasonably sound in his diagnosis he is far more likely, and far more ready, to accept his diagnosis and operate, however much the clinical picture has brightened. This ideal has been a happy feature of the smaller county hospitals and should be preserved. I have enjoyed the most excellent relationship of helpful co-operation at all times, generally late at night and in the early hours of the morning!

Pathological investigation plays a minor part in deciding the presence of an acute abdomen, but there are rare occasions where it does help with the differential diagnosis, and laboratory facilities should be readily available to the family practitioner. The accessibility of the laboratory should be preserved and any attempt to prevent or discourage the family doctor from availing himself of this directly should be discouraged. I had the questionable privilege of seeing my surgical colleague with a typical retrocæcal appendix—pain awaking him from sleep in the early hours of the morning which persisted until I saw him at midday, he had vomited once, there was deep tenderness in the right iliac fossa, a furred tongue and the unmistakable appendix breath. I told him that he had a retrocæcal appendix, an opinion which he found difficult to believe because the pain did not seem severe enough. He was not convinced until we had a leucocyte count done and a total of 19,000 placed before him. He capitulated, and at operation the appendix, as it was being removed, burst, and its contents hit the flow meter on the anæsthetic machine!

In yet another case laboratory assistance was invoked. This was in a boy of 11 I was called to see in a farm late at night. He had been ill for two or three days with pain in the side, he had a temperature of 103° F. and was exquisitely tender in the right loin. I made a diagnosis of pyelitis or perinephric abscess but was not impressed by this and told his father that he might well have a high retrocæcal appendix abscess. Due to transport difficulties I temporized and instructed his father to go in a neighbour's car early the next morning with a letter from me and a specimen of urine in a bottle suitably sterilized. I had the report at 10 a.m. by phone, saying there was nothing in the urine. I was now certain that he had an unusually high retrocæcal appendix abscess and went out 7 miles to see him and sent him in with this diagnosis, mentioning the negative findings in the urine. But even so, the clinical picture was confusing and operation was delayed thirty-six hours. I was grateful for the prompt co-operation of the laboratory in this case.

Transport was always difficult in the country, but the establishment of an ambulance service has solved this problem. Frequently at night I have taken my own cases into hospital, especially cases of perforation. Two years ago at 3 a.m. on New Year's Morning arriving home after a Territorial Ball I was presented with an anti-climax in the form of a call to a place 9 miles away. This is a form of irritation undoubtedly familiar to us all. However, the man proved to have a perforated duodenal ulcer—he was a typical case, rigid as a board and complained of "rheumatism or something" in his right shoulder. I gave him ½ grain morphia and took him in my car with his wife 18 miles to hospital and saw that he was operated on with the least delay and arrived home at 7.20 a.m. having done 36 miles.

Another occasion I was called about 1 a.m. to a cottage 7 miles away to a woman with acute gall-stone colic, gave her ½ grain morphia and whilst waiting to ensure that this took effect sat down in the kitchen and the husband complained to me of indigestion. I eventually got home, got to bed and went to sleep. About 4.30 a.m. I had a telephone message once again asking me to come up immediately because "something terrible had happened to father"—I immediately thought of perforation. This was soon confirmed. I gave him a ¼ grain morphia, put him in my car and took him 16 miles to hospital and at 7.30 a.m. was assisting at the operation. I had travelled 39 miles for that little family during that night. Accepting responsibility for transport is not without its reward for the case just described provided me with my Christmas turkey for many years afterwards!

There is, of course, the odd case one usually meets with in a rural practice who refuses to be transported. Within a few weeks of entering practice, my old predecessor took me to see a farmer of 68, whom he had been attending for the past fortnight suffering from a large growth of the cæcum. I thought it was a large appendix abscess filling the right iliac fossa, for there was a suspicion of redness and œdema of the skin of the abdominal wall. The patient refused to go into hospital and although his daughter, a theatre sister in a county

hospital, who was recalled home the next day, tried to persuade him he point blank refused to have the knife, but would agree to anything else. I asked the old doctor to give an anæsthetic, I made a small snick through the skin, and put in a large trocar and cannula attached to a Potain's aspirator and took off about 3 pints of thick pus. The right iliac fossa collapsed, the temperature settled, and the old farmer immediately got better and was up in ten days and in no time was hale and hearty driving his trap once again, little realizing that his debt to Providence was greater than to me. Seven months later I had a telephone message one Sunday morning from a surgeon 60 miles away saying that this old farmer was on holiday there and had an acute appendix but refused to go into hospital unless I came up and told him so. I felt it was my duty to go, and subsequently persuaded the farmer to have his operation at which I assisted. At operation we saw a typical inflamed œdematous appendix with a fæcolith near the tip. In addition, attached to the appendix there was an unusual structure 3 in. in length exactly like a collapsed toy balloon.

Appendicitis

The incidence of acute appendicitis so overwhelmingly outnumbers the sum total of all the other surgical emergencies in general practice that in this condition only can one feel justified in having definite views.

History.—When called in we generally know the patient well, his family history, his background, his standard of intelligence, his reaction to past illnesses, if any, whether he is a good type or a nervous type, and the reaction of other members of the family to the patient and this sudden crisis. This knowledge enables one to assess the degree of pain more confidently than if he were a stranger. The pain so frequently begins in the small hours of the morning, and wakes him from sleep; this is a clinical impression formed from the number who do commence in this way and it is presumptive evidence of an acute condition. The pain, at first vague and ill-defined, situated in the epigastrium or umbilical region, gradually increases in severity, and vomiting generally occurs in a few hours, commonly once only, or perhaps repeated, as the pain gets worse towards breakfast time or mid-morning, the pain meanwhile moving down to the lower abdomen. This condition is tolerated by the patient until the evening and most commonly it is then that the doctor is sent for.

Vomiting is an important symptom. In the usual straightforward case it is invariable and occurs about once only, but if repeated, then the case is probably one of obstructive appendicitis and likely to go on to perforation. Thorek (1949) says "Nausea and vomiting have been impressed upon us as being associated with appendicitis. This is the exception and not the rule. Anorexia, or loss of appetite, is more constant and more important than either nausea or vomiting." Now this is probably true of the mild initial attacks which we do not see, but hardly describes the typical attack with which we are generally faced. Cope (1921) is nearer the truth in saying "Nausea and loss of appetite are induced in many people who do not vomit."

Examination.—Whilst taking the history, a most constant and striking sign is frequently noticed and that is the unmistakable smell of the breath. Next I take the *Temperature* and *Pulse*, and most constantly of all they are usually normal, for fever is not an early finding; frequently the temperature is 98·8°–99·4° but with a normal pulse-rate. Fortunately when I left hospital I had this firm resolve in my mind that a normal temperature and pulse should not mislead me in the differential diagnosis. I saw as a resident and I have continually seen with my own cases, which I nearly always attended at operation if they occurred at night, so many gangrenous appendices with normal temperature and pulse. This amply illustrates the importance of seeing one's own case of acute abdomen at operation, whenever possible. If the temperature is 100°–101° or more, then it is a sign, not of appendicitis, but probably of a localized peritonitis. In the old days it was common to wait for this rise of temperature before feeling justified in making the diagnosis. On the other hand, where there is no temperature the inexperienced may attribute the pain erroneously to an intestinal or mild renal colic.

Next I look at the tongue and smell the breath. The tongue is usually moist and furred to varying degrees and the breath very unpleasant and peculiarly foul. I consider that it is one of the most important signs we have, and I have always attached as much if not more importance to it, in the presence of a typical history and pain in the right iliac fossa as any other sign or symptom. To me it is a sign of the need for urgent operation. It is very striking, and should be recognized quickly and surely. In hospital I got to know the typical abdominal breath, the appendix breath, "the *B. coli* smell", and I have carried this impression with me into general practice. I have always made a habit of looking at the tongue of every patient and smelling the breath of everyone complaining of abdominal

pain. It is only by making a routine practice of this that one develops that sense of smell, which, on entering the sick room, may be strong enough to suggest the diagnosis. Frequently the examination has to be made by candlelight or lamplight, or a light from a small dormer window in a low bedroom, but I sometimes feel I could diagnose an appendix in a dark room in a dumb patient. I place the highest value on this sign which makes its unmistakable appearance before any change in the temperature or pulse-rate. What the explanation is, I cannot pretend to know, but is it more than coincidence when frequently the same smell comes up from the opened abdomen?

Examination of the abdomen.—After kneeling by the bedside and observing the abdominal movement and taking note of its contours, I than palpate in the usual way. Proceeding from wide to localized, from superficial to deep, from painless to painful, I first estimate the degree of tone in the upper rectus very gently, and compare both sides; slight differences in rigidity or guarding are important when present, but this sign is often missed if palpation is not done very gently. This, and rigidity over the right iliac fossa, is an inconstant finding, however, which depends in the case of a normally situated appendix, upon the stage at which the patient is seen. In the early stages there may be no guarding whatsoever, but later on guarding is present and may even pass off again later when perforation has occurred for some hours. We must also remember the innocent appearance of the abdomen with a pelvic appendix. Palpation is performed, then, lightly at first, then repeated more deeply. Deep palpation in the left iliac fossa generally produces discomfort or pain in the R.I.F. in a true case and frequently pain on release of pressure. If there is no increase in pain in the R.I.F. when palpating deeply in the left and exerting a fair amount of pressure with the flat of the right hand I then always press firmly with the fingers of my left hand over McBurney's point, and there is generally no doubt about the response. Release or rebound tenderness is sometimes elicited and is very striking when present and clinches the need for operation.

The ilio-psoas test is very helpful in the case of a retrocæcal appendix but, if negative, firm palpation with the fingers of the left hand over the R.I.F. frequently brings out a tenderness not noticed before. Comparison of the two flanks for muscle guarding is also worth doing and on rare occasions an increased tone can be detected in the right flank when the appendix is retrocæcal and higher than normal.

Examination of the chest is useful, but examination of the back more so when the patient's reaction to sitting up may be judged. After examining the lung bases I always, whilst sitting on the bed behind him, palpate his abdomen with both hands. Relaxation is better and palpation easier. Rectal or vaginal examination also is done, and the urine examined in a case where I am not reasonably certain.

Difficulties in Diagnosis of Appendicitis

Difficulties in diagnosis are made *especially so* in the presence of another condition. Cases I and III are the only two in my experience that can be entirely attributed to my failure and they stand out as crosses in my memory.

Case I.—A farmer, aged 60, who lived in an area where there was a localized outbreak of Sonne dysentery had diarrhœa for three days and I saw him on the third day. His history of pain was vague, the abdomen was very slightly distended, no rigidity, and slight tenderness suprapubically. A rectal examination was not done for I assumed he probably had a Sonne infection. I gave him sulphaguanidine. Next day, the lower abdominal tenderness had increased. For the first time a possibility of a perforated pelvic appendix went through my mind, but because of the Sonne query a rectal examination was again not done. I took a sample of blood and fæces and took them to the laboratory that afternoon myself. The following morning I got the result by telephone. Fæces negative, leucocytosis 17,000. He was sent into hospital and operated on. He had, of course, a pelvic abscess, eventually developed an ileus paralyticus, later a residual abscess, was reopened and gradually went downhill and died after six weeks. I had started wrongly by assuming the case was a Sonne, the abdominal signs after three days were confusing, and even after considering the possibility of a pelvic abscess I did not do a rectal examination. The laboratory investigations were helpful but belated and should have been unnecessary.

Case II.—Two other cases of an acute appendix in the presence of a gastro-enteritis I can look upon with more satisfaction, one in a woman, and the other in a man. The man aged 40 was the second acute abdomen I saw in practice. He had a history of abdominal pain for twenty-four hours and like the rest of the family had vomited and attributed it to pork eaten the previous day. He had taken castor oil that morning, the pain got worse, and when I saw him at 6 p.m. he was better—temperature and pulse normal, typical tongue and breath, very slight guarding of the upper right rectus, slight tenderness in the R.I.F. I told him he had a perforated appendix and that he must go into hospital, he protested that he was now better and that the rest of the family had the same thing. But I was firm and he agreed to go. I went up for the operation at 10 p.m. and discovered that the opinion there was against an acute abdomen. I saw him in the ward looking extremely well, sitting

up and protesting vigorously. I examined him and could find nothing amiss, no rigidity, no tenderness, nothing except the smell of his breath. I felt it was now, or never, and because of my insistence the surgeon operated. My fears were correct. Had I been called to see him at 10 p.m. when all signs had passed off, and not at 6 p.m., then, chastening thought, I am afraid I would have missed it. This taught me a very valuable lesson to make my diagnosis at the first visit, especially necessary in a country practice, and not to wait and return some hours later when there is just as much likelihood of the clinical picture becoming more confusing rather than clear. This, I think, is of real importance.

Case III.—This was a case of a young married woman of 24 with an acute abdomen in the puerperium. She had a spontaneous delivery and on the fourth day developed severe abdominal pain and vomiting. She had an appendicectomy eighteen months previously, and the possibility of an acute intestinal obstruction due to a band crossed my mind, but she had her bowels opened after the attack and I dismissed the diagnosis and thought of other possibilities such as thrombosis or a parametritis. Next morning she was still vomiting off and on, and there was nothing in the abdomen suggestive of an obstruction, but I ordered the district nurse to give her two turpentine enemata with a two hours' interval. That night on visiting her I was told that she had a good result from both, and I felt satisfied that she had some other condition and that I would send her into hospital in the morning. I received an urgent call at 6 a.m. and on my arrival discovered that she was dead after violent bouts of vomiting during the night. I did a post-mortem in the cottage with the help of a technician from the laboratory. I found no band of adhesion, but an internal strangulation of 5 ft. of jejunum through a small opening in the mesentery. Now it all seemed so obvious, and the misleading enema results and complete lack of distension so easily understood.

In the puerperium with a large uterus present, and already some distension, one hesitates to think of another pathology, and although in the face of the recent appendicectomy and the possibility of a band I could not even then make her fit the diagnosis. We are fully aware of the difficulties of diagnosis in the early case of intestinal obstruction, but in the puerperium where so many things may, and do go wrong, or, in the late stages of pregnancy, it can be especially difficult. It is important to determine the nature of the abdominal pain, especially again in labour or abortion, where deviation from the normal sequence may give the clue. Deviation from the normal sequence of (*a*) Contraction in the uterus felt by the doctor. (*b*) Pain in the uterus experienced by the patient and still felt. (*c*) Pain has passed off, but the contraction still detectable for a short time.

This is a description of the typical labour pain and any deviation from this should make one suspect disordered uterine action or an extra-uterine lesion. Matthews and Mitchell (1948) stress the difficulties of an early diagnosis of intestinal obstruction in relation to pregnancy. They record two cases and in the first the diagnosis was late; the second case occurred soon after, and with the experience of the first the diagnosis of the second was made earlier.

TABLE I.—TOTAL EMERGENCIES IN WHOLE PRACTICE: FIVE-YEAR PERIOD 1946–1950

Year:	1946	1947	1948	1949	1950	Totals
Acute appendicitis ..	16	17	20	18	16	87 {42 (f) 45 (m)
[Perforated appendix	—	3	—	3	1	7]
Strangulated hernia ..	1 (m)	—	—	4 1 (m) 3 (f)	1 (f)	6 {2 (f) 4 (m)
Gall-bladder	1 (f)	2 (f)	1 (f)	2 (f)	—	6
Perforated gastric ulcer	—	—	1 (m)	2 (m)	1 (m)	4
Salpingitis	1	1	1	1	—	4
Intestinal obstruction..	—	1 (m)	1 (m)	1 (m)	—	3
Diverticulitis	—	—	1 Meckel's	—	2	3
Peritonitis	1	—	—	1 T.B. (m)	—	2
Renal colic	1 (m)	—	1 (m)	—	—	2
Ectopic	1	—	—	—	1	2
Pyelitis..	—	—	—	—	2	2
Twisted ovarian cyst..	—	—	1	—	—	1
Undiagnosed	—	—	3	1	2	6
Total	22	21	30	30	25	128

Appendices to total emergencies, 68%.
Incidence of acute emergencies, 0·35%.
Incidence of acute appendix, 0·24%.

TABLE II.—ANALYSIS OF CASES OF ACUTE ABDOMEN TEN-YEAR PERIOD 1941–1950
OWN CASES

			Total	Died
Appendicitis	(i) Clean sutured	29		
	(ii) Perforated on laparotomy	9		
	(iii) Abscess (Ochsner-Sherren)	5	43	6
Cholecystitis	(i) Cholecystectomy	4		
Gall-stones	(ii) X-ray N.A.D.	1	5	
Intestinal obstruction	(i) Resection	3		
	(ii) N.A.D.	1	4	2
Perforated peptic ulcer	Laparotomy	3	3	
Strangulated hernia	Herniorrhaphy	3	3	
Ruptured ectopic	Laparotomy	3	3	
Salpingitis	(i) Chemotherapy	2	2	
Diverticulitis	(i) Meckel's (op)	1		
	(ii) Chemotherapy	1	2	
T.B. peritonitis	(i) Laparotomy	1		
	(ii) Conservative treatment	1	2	
Abdominal pain—no diagnosis	Sulphaguanidine	2	2	
Pyelitis of pregnancy		1	1	
Renal (? colic)	Conservative treatment	1	1	
Perforated diverticulum of bladder	Laparotomy and repairs	1	1	
		Total	72	

Appendices to total emergencies 60%

"The acute abdominal emergencies are the touchstones by which our worth as doctors is judged. When we meet them we must be prepared to sacrifice our labour, even our reputations; but we should remember that the one sacrifice for which there is no atonement is the sacrifice of time. It is better to be certain than to be right. Mistakes are nothing to be ashamed of if they are not due to laziness, to carelessness, or to the fear of making them."—Ogilvie (1947).

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Mr. A. Dickson Wright: The phrase "acute abdomen", although to the purist grammatically repugnant, is a vivid and useful term indicating the acute need for early diagnosis and operative intervention. Like faucial diphtheria, acute osteomyelitis and infantile paralysis, it is a spectre which haunts the days and nights of the general practitioner for it is he who has to set the diagnostic ball a-rolling; a little vacillation and a family is broken up or from what ought to have been a simple illness, a long-drawn battle for life with maybe invalidism at the end.

One yearns for dogmatism, but it is dangerous to pontificate with categorical clichés because the exceptions are not so exceptional. Take the useful slogan that "a perforated peptic ulcer lies gripped as in a vice and is never restless" and it will lead to a disaster such as this:

A young artist of 28 of artistic appearance and dress walked into the casualty department demented with abdominal pain of sudden onset. He was so restless that examination was difficult and in his agitation he bit the thermometer in two. He engendered hostility in the casualty surgeon, who, remembering the dictum about restlessness, dismissed him as a case of artistic temperament, and charged him eighteenpence for the broken thermometer and sent him home. The next day he was back and his abdomen found to be awash from a perforation. A subphrenic abscess and an empyema carried him off a week later and the world may have lost another Picasso.

The nearest I can get to a comprehensive safe statement about the acute abdomen is that violent abdominal pain is surgical and by this I mean pain that stops everything, even thinking. The pains of gastric influenza, of dysentery, of tabetic crises, of spasmodic colitis, of shingles, of hepatitis, of diabetes and of chronic pancreatitis are not of this order; unfortunately it is the appraisement of the degree of pain which demands clinical experience and may be slow in coming to one.

It occasionally happens that the pain of acute thoracic medical conditions spreads into the abdomen and this includes the following conditions: (1) Coronary infarction. (2) Diaphragmatic pleurisy. (3) Acute pneumonia. (4) Acute heart failure with suddenly engorged liver and tense capsule. (5) Epidemic phrenitis (Bornholm disease).

To cover these cases there is an aphorism—"the medical case sits up, the surgical lies flat"; with the usual reservation this nearly always serves. Uræmia can simulate everything and it may be mistaken for intestinal obstruction with distension, vomiting, constipation and dry tongue.

Acute abdominal conditions for which, although surgical, yet operation is harmful to the patient.

Pride of place must be given to the renal colic which has led to more reputations being ruined or gained than any other condition. Here there is no doubt about the violence of the pain, it may be *heard* occasionally before entering the house; the patient is incoherent with pain and will agree with alacrity to any operation one cares to propose. His abdomen is frequently distended, fluid bowel levels may show in the X-ray, rigidity and tenderness may be present and the pain may be all abdominal with no renal quotient and the vomit may be black, brown or bilious. When this condition descends on a doctor, a surgeon and even on a urologist, in my experience they seem incapable of diagnosing themselves because the pain stops all thinking; their only anxiety seems to be to make a will and get on an operating table as soon as possible. The general practitioner may find a clue if in every case of acute abdominal illness he thinks of the urine, the surgeon if he has a plain X-ray done with special regard to a stone in the lower end of the ureter and if his suspicions are strong or he encounters opposition to his diagnosis, there may even be a chance to do an excretion pyelogram or a cystoscopy. If a negative laparotomy is carried out and the tense distended ureter is found, the honest man will pass a ureteric catheter at the completion of the operation, making what excuses he can for the laparotomy.

Second place in my opinion must be given to the Mittelschmerz of the older schoolgirls with some intra-abdominal bleeding. There is rigidity, temperature and sometimes sickness. The tendency is to diagnose appendicitis and to find on opening, blood-stained fluid of varying amount in the peritoneal cavity with a recently ruptured graafian follicle. Undoubtedly these cases are better left alone as twenty-four hours in bed seems to put them right.

Acute pancreatitis always does better if left alone except for morphia, splanchnic block, insulin and blood transfusion in occasional cases. The history of gall-bladder trouble helps the diagnosis as does the sugar and diastase in urine or plasma. The vomiting is generally violent, noisy and unproductive and the abdomen is not so rigid as with the perforation that the degree of pain would suggest. There may be bruising in the left flank and around the umbilicus.

Acute diverticulitis is best left alone and responds promptly to chemotherapy of the bowel contents (Sulphasuxidine) and systemically (sulphonamides, streptomycin, Aureomycin or Chloromycetin). It is a difficult diagnosis to make, the patient is often obese and elderly and there is a suspicious history. The pain is more to the left than the right of the mid-line and there may be a vague tender mass present.

Salpingitis is best left alone to chemotherapy and rest, but the diagnosis from appendicitis may be difficult. The pain in salpingitis starts low and ascends and the signs of gonorrhœa or history of abortion may be discovered. There is also a tendency for the pain to descend into the thighs as in all tubal and ovarian conditions. The stigmata of looseness in the fair sex vary from age to age and the clinician's knowledge of the world and human nature will serve him better in this diagnosis than his medical training. Operation for this condition has often had many unhappy sequels and should be avoided.

Pyelitis in pregnancy is important and for some reason resembles appendicitis more than pyelitis, at other times, possibly because of the dilated infected ureter and the fact that the urine often contains no pus, merely a shimmer of organisms.

To operate unnecessarily for appendicitis in pregnancy is very regrettable, but to miss the condition is worse and, in my own experience, I have operated on appendicitis at all stages of pregnancy, on one occasion while labour was in progress.

The full bladder has been mistaken for twisted ovarian cyst and volvulus, remembering it is not always in the mid-line, especially in children. An operation performed for this condition is probably the crowning humiliation of a surgeon's life. A full bladder is the only abdominal tumour which when squeezed produces a desire to micturate.

The abdominal malingerer scores as many successes as there are scars on the abdomen. By sheer persistence she often achieves oblivion, as pointed out by Wrigley in his description of the "abdominal woman".

As regards the abdominal emergencies, acute appendicitis, cholecystitis, the perforations, the torsions and the strangulations and the obstructions and the mesenteric thromboses,

there is always the acute onset during which the patient is floored by the pain, but unfortunately in all of them this is followed by a period of remission of symptoms during which time complacency may lead to disaster. In the gastric and duodenal perforations after the first agony of the impact of the acid juice, and this may be felt as far away as the penis or vagina, the acid is then absorbed by the peritoneum and pain, rigidity and tenderness diminish until they return with the development of infective peritonitis. In appendicitis, the sloughing of the appendix diminishes pain because the nerves slough too or the perforation of the appendix diminishes the tension inside the organ and there is a dangerous lull till the peritonitis becomes established. In strangulations and torsions, the bowel and mesentery or pedicle slough and nervous conduction ceases. In obstruction the bowel wall above the stoppage becomes waterlogged and stops contracting and so the pain ceases, peristalsis and borborygmi disappear and diagnostic delay is engendered. This lull is a very real danger in all abdominal emergencies; morphia and a wait till the morning may lead to tragedy. This will be avoided if one remembers that the severe abdominal pain of the onset is usually surgically significant.

In appendicitis, the very young, the obese and the aged patients provide the difficulties. In the very young one feels like a veterinarian because the patient can tell you so little, in the obese one's hands can tell so little and in the aged one's wits seem to wilt. In the cases of the acute abdomen when the discovery of a lump would clear up the difficulty this is often found by the simple manœuvre of giving a full dose of morphia to the patient and palpating again when apprehension and guarding have disappeared. This I have found very valuable in appendicitis as well as diverticulitis, salpingitis and ectopic gestation and strangulation and volvulus. The pelvic appendix is of course the worst diagnostically and prognostically, the pain is often far away and atypical and rectal examination in a large feather bed is not a very conclusive procedure. In this respect there is one dogmatic statement that can be made: "the only rectal examination that counts is the one you make yourself."

In intestinal obstruction there is one slogan that concerns the rectum and the hernial orifices (this includes the navel): it is the most incontestable statement, but unfortunately it is so often forgotten. Moreover, the hernial orifices are often deep in adiposity and the periumbilical geography very confused, so that much more than inspection of the hernial orifices is required.

Though the use of X-rays increase the precision of diagnosis in acute abdominal emergencies I know that is often hard to come by, but on occasion it may be available with only slight difficulty and yet not used. The discovery of a ureteric stone, the crescent of gas in the peritoneal cavity, the fluid levels in the intestine, the balloon of gas in volvulus or strangulated loop may be so much pure diagnostic gold, but again like everything else in the hard diagnostic world, even X-ray appearances may lead astray.

In intussusception, often so easy to diagnose, often so treacherous, the help of a barium enema on the sedated child will clear the whole problem and end all the head shaking and vacillation of the series of consultants who are called to the puzzling child.

As with biochemistry, so with radiography, there is great danger if they are allowed to diminish clinical judgment, engender delay and lead to humiliating disaster.

One last aspect of the subject must be mentioned, namely, how is one to deal with the case of acute abdomen that refuses operation. I have found that the giving of a good dose of morphia will sometimes bemuse the patient so that he does not know if he has consented or not. The fear of cancer may also be used by hinting at this as a possibility.

In young girls with appendicitis, one only has to breathe that pelvic appendicitis may engender sterility and all parental opposition disappears. This occurs even with the plainest and most uninspiring individuals; it would seem that the desire to perpetuate is a basic instinct in all. Sometimes other family circumstances can be exploited, a devoted wife or other relative or acquaintance will turn the balance in the surgeon's favour. On one occasion I stooped to the artifice of saying that the wife opposed the husband's operation; this caused him to insist that she had no right to interfere in his affairs and he withdrew his stubborn refusal, was operated upon and recovered and they lived unhappily ever afterwards.

[*March* 21, 1951]

DISCUSSION ON HEADACHES

Dr. G. J. V. Crosby: At 6.45 on a fine summer morning last year, I was summoned urgently to see a middle-aged pharmaceutical chemist who had wakened at 5 a.m. with an intolerable headache. I found him prostrated but fully conscious. He had recently been suffering from headaches which he attributed to his eyes but they had not been serious enough to seek advice and he had doctored himself with reasonable success. This, however, was such a headache as he had never before experienced. He had vomited and the pain had subsided to some degree but was still severe. The pupils were small and reacted sluggishly and he had some rigidity of the neck. Plantar reflexes were doubtful but that on the right side appeared predominantly extensor. The pulse was slow. Obviously there had been an intracranial calamity and a leaking aneurysm seemed a possibility. Unfortunately he did not make the journey to hospital as he suddenly went into epileptiform convulsions, with extreme neck retraction and expired in a matter of minutes. Autopsy that afternoon showed an extensive subarachnoid hæmorrhage.

This was the most dramatic instance I could recollect when considering cases of headache occurring in my own practice during the past year or so. But, the comparative rarity of conditions of this type made me feel that here was not a true example of headache in a commonly presenting guise. So I returned to my case book. Here are three more short histories.

Some five months ago I was consulted by a man of 45 who complained of severe morning headaches, usually, but not always, unilateral. They had been increasing lately, both in duration and intensity and now lasted regularly twenty-four hours culminating in nausea and vomiting. On questioning, he described a typical aura of indistinct vision in one-half of the field accompanied by flashes of light. It was easy to diagnose migraine.

Two or three weeks ago a patient came to me complaining of severe recurrent frontal headache. Full examination revealed very little of an objective nature and he had no error of refraction. There was, however, a very slight inequality of antral transillumination and neither side lit up really well. Treatment directed towards draining the sinuses effected a surprisingly rapid and complete cure.

During the past three months, I have been treating a case of severe arterial hypertension with hexamethonium bromide. This patient's pressure headache was making life intolerable. It is of interest that, while the sphygmomanometer readings have only fallen slightly, the general sense of well-being and lack of headache are now out of all proportion to objective findings.

Here then are four cases of headache, picked at random from my own experience during the past eighteen months, and how different in type and origin they are. It is clear that any introduction to the discussion of so wide a subject cannot possibly cover every aspect of the incidence of the symptom in the time available unless one confines oneself to a mere repetition of tables of classification. In spite of that, it is difficult to avoid considering the symptom under certain headings or types.

In the first place, cases of headache may be immediately divided into two types, those in which the patient is complaining mainly or entirely of the symptom itself and those in which it is obviously incidental, for example, a result of fever, following a blow on the head, or the sequel to undue celebration the previous evening.

There are undoubtedly many types of headache in which the diagnosis is immediately clear, but all cases, in spite of that, demand approach by careful questioning and I know no other complaint in the investigation of which this yields better dividends.

It is wise, however, to adopt a systematic scheme.

Firstly, in which part of the head is it felt? Is it continuous or intermittent? What is its particular characteristic—for example, would it be described as dull, throbbing, bursting, blinding, piercing, burning or like a band round the head?

Is there any suggestion of an aura? How long do the attacks last? Are they of long standing? How old was the patient when they began and have they been growing in intensity

of late? Is it a morning headache or particularly felt at the end of the day when mentally or physically fatigued? Is any postural factor involved?

Is the headache the sole complaint or is it associated with other symptoms such as nausea, vomiting or giddiness, general malaise or insomnia? Is it, in fact, bad enough to prevent sleep? What is the nature of the patient's employment? Does it involve eye-strain? Is there any history of injury, either recent or in the past? Does the pain follow recent nasal catarrh or is there any other nasal, aural or dental trouble?

The importance of full physical examination is obvious and this must include urine, ophthalmoscopy, and estimation of blood pressure. Lastly, I always search for "trigger points" not only in the scalp itself, but in the neck, along the ligamentum nuchæ and elsewhere.

The Types of Headache

In the case I first described, I gave a short account of one type of headache due to increase in intracranial pressure. In effect, the headache of increased pressure may be very variable in site and in character. In cases of intracranial tumour, I would say that the pain is usually described as throbbing or bursting and may be referred to any part of the cranium and is very often occipital. I remember a case of a young man, who had been in very poor shape for a considerable time but had refrained from taking advice in view of his approaching marriage. On his honeymoon he complained of very severe occipital headache and the following day was practically unconscious. At operation a subtentorial growth was found and he died within two days. Pressure headache is not necessarily due to a neoplasm or intracranial abscess. That of high arterial tension may give very similar symptoms and physical effort and changes of posture are particularly liable to accentuate the severity of the pain. Ophthalmoscopy is helpful in differential diagnosis, though papillœdema may not necessarily be present until quite a late stage.

The headache of the infectious disease is, as I have already said, usually fairly easy to diagnose as it is generally accompanied by other symptoms referred to the particular infection and, to my mind, in the great number of cases bears a direct relationship to the degree of fever present, though headache may be the presenting symptom in typhoid fever before the temperature rises. Generally, the pain is continuous and throbbing and occupies the whole cranium or is referred particularly to the frontal area. I suppose we have all of us met a large number of cases with headache of this type during the recent influenza epidemic. Then we have those individuals with fever, malaise, nausea and blinding headache often referred to the occiput, whom we have also most of us met during the past four or five years and who have eventually proved to be suffering from poliomyelitis or rather polio-encephalitis.

While considering the toxæmic type, attention should, I think, be called to an easy error in diagnosis. Severe headache can be one of the earliest symptoms in uræmic states. It is therefore absolutely essential not to miss urine examination where there is any possibility of nephritis—especially in cases presenting a high arterial tension. Once again the importance of examining the discs has to be emphasized.

Perhaps one of the commonest causes, and one which, I believe, is often confused with migraine, is what must still be called the "fibrositic" headache. I believe that in many cases painful nodules and trigger points may be found not only in the scalp itself but frequently in the cervical muscles, which are the determining cause of nagging, aching headache, often continuing for a long time with periods of exacerbation alternating with relief. A very useful point in diagnosis is that sudden movement, coughing and sneezing aggravates the pain. The headache is frequently unilateral. Deep palpation suboccipitally may cause shooting pain along the course of the greater occipital nerve, a point which is practically diagnostic. In such cases I have had some success with local anæsthetic injections and no doubt skilled cervical manipulation is helpful, with the precaution of preliminary X-ray.

It is important to enquire whether cases of this type have vertigo. The headache of Ménière's syndrome has certain similarities and is often referred to the suboccipital region on the affected side.

Some years ago, I was involved in the examination of large numbers of post-traumatic cases for an Insurance Company. It was only then that one realized the very high incidence of the neurasthenic headache, especially among those hoping for considerable compensation and who felt that work was eminently undesirable. The use of the word "agony" in the patient's description of his disability often goes a long way towards helping diagnosis. This does not necessarily mean that the symptoms are not very real. There is, however, a certain vagueness of description which may be pathognomonic—for example "my head feels like a lump of wood". "It's all numb and it feels as though there is a band round it" and so forth. This is in contradistinction to the sharp pain due to nerve involvement or

the bursting pain of increased intracranial pressure following injury. Remember also that the neurasthenic headache is usually associated with concurrent complaints such as anxiety, insomnia, depression or lack of concentration.

I do not wish to give the impression that all neurasthenic headaches are necessarily traumatic. We all of us who have practised for a good many years, know only too well how commonly they are met in our everyday routine, and without any easily determined cause.

The headache due to affections of the ear, nose and throat are fairly easy to distinguish. Otitis media of itself does not usually cause a true headache and if present it is probably due to extension of the infection. In these days we do not see the mastoids, the extradural abscesses or the cerebellar abscesses, at one time all too common. But there is still the possibility of their incidence in neglected cases. On the other hand, we do still see patients in whom the symptom is due to sinusitis, especially of the frontals and ethmoids. Diagnosis may be confirmed by transillumination and X-ray with positive results but negative X-ray results do not always exclude the possibility of a " vacuum headache " due to absorption of air behind blocked outlets.

The pain in the head due to sinus trouble can be confused with that due to eye-strain and vice versa. Both are generally referred to the frontal and orbital regions, both may occur early in the day, both may be dull, throbbing or neuralgic. It may need very careful questioning to differentiate the two. Examination of the teeth is also essential. Incidentally, an elderly woman patient of mine who was operated upon for chronic glaucoma eighteen months ago informed me that one of her greatest reliefs was that her one-sided neuralgic headache had ceased.

I am left with what is, from the ætiological and the therapeutic points of view at all events, probably the most difficult of all types of headache, namely migraine. Diagnosis is usually not very difficult. The headache has a paroxysmal onset, starting often as a dull ache and working up to an incapacitating and persistent throb; its generally unilateral distribution (though this is not always the case) and the presence of a preceding aura are fairly constant phenomena. When there is a history of the pain culminating in a climax of nausea and vomiting, which does *not* bring about relief, the diagnosis is fairly clearly clinched. The "aura" is interesting. Descriptions of "fortification figures", appearances of rain and so forth are, I believe, only very rarely met in actual clinical experience, in fact I can only recollect one case in recent years in which the patient described anything approaching them. One has, however, more often heard the complaint of cloudiness of vision and flashings of light. More generally I believe that the so-called aura is little more than a distinct awareness that "one of my heads" is on its way. I think it may also be remarked that the intensity of the attacks is very variable. This, I suspect, has a good deal to do with the sufferer's general condition at the time. I have little doubt that emotional disturbance and worry have a distinct bearing on the frequency and severity of incidence. Moreover, the sufferer from migraine is, in 90 cases out of 100, of a distinct "type", the type in fact in whom one would expect to find allergic manifestations or duodenal ulcers, sensitive, intelligent, conscientious and spastic.

In the past, treatment has been conspicuously ineffective and ordinary aspirins, phenacetins, caffeines, Cachets Faivre and the like are disappointing. Ergotamine tartrate is undoubtedly useful in aborting attacks—up to 0·5 mg. given parenterally. But I have known this produce nausea and vomiting almost immediately following injection and I, for one, certainly view the intravenous route with considerable misgiving. Orally, absorption is somewhat uneven and I now advise patients to allow the tablets to dissolve under the tongue. Recently, however, dihydroergotamine has come into vogue and, from personal experience, I feel this may be highly recommended. I have not found it necessary to give the drug by injection, though even by this route it is remarkably free from side-effects. Usually 20 to 30 drops of the solution by mouth, repeated hourly until relieved, is all that is necessary. It should be made clear that ergot derivatives in no way prevent or lessen subsequent attacks.

On the supposition that migraine is due to spasm of the cerebral arteries, and particularly those of the scalp and dura, it has been suggested that parasympathetic stimulants should be effective. Carbachol and Prostigmin both seem to have some value and it is now my practice to prescribe one or other of these to be taken over a fairly prolonged period. My general impression is that they have their use. It seems possible that the sympathicolytic substances such as Priscol, hexamethonium bromide and perhaps even nicotinic acid might well be tried, but I have no experience of them in this condition and can find nothing in the literature.

Finally, on the hypothesis that many women suffering from migraine show signs of menstrual disturbance with excessive loss, the administration of progesterone has been advocated in doses of 5 mg. or more on alternate days. It is clear that the menstrual invalid

is liable to headache associated with almost any other symptom, but unaccompanied by physical signs. Whether then, the glandular assumption is an explanation of true migraine, there is considerable doubt. We do know that in a certain percentage of women, water metabolism is greatly disturbed in the few days preceding the onset of menstruation, as shown by an actual increase of weight of some pounds, and enlargement of the breasts which is measurable. Headache of a migrainous type may be, and frequently is, an associated symptom. It seems possible that this group may account for the small superiority of incidence in females. It is certainly true that cases of this type show a great improvement if treated with ammonium chloride, restriction of fluid and a salt-free diet or at any rate by reduction of intake of the sodium ion. A small dose of a mercurial diuretic probably has a similar effect.

There is one small difficulty which presents itself in accepting this as definite cause for headache, namely that the water retention of pregnancy, which is even greater, has not a comparable effect.

Dr. Desmond Curran: In order to ascertain more precisely the frequency of headaches or of head complaints in psychiatric practice, I have gone through a random sample of 150 cases seen in private and of another 150 cases seen at St. George's Hospital in the year 1948. In approximately 80% of this series of 300 cases an independent history was obtained from friends or relations.

My routine has been to say "Would you mind starting this way. What are the main symptoms that trouble you?" and then to write down the replies.
I have tabulated the results so obtained.

TABLE I

Diagnoses	Total No. of patients	No. of "Head Complaints"
Depressions	83	32
Anxiety states	63	35
Hysteria	37	16
Schizophrenia	26	12
"Psychopaths"	18	7
Sex problems and perversions	13	2
"Organ neuroses"	12	1
Dullards	11	3
Organic reactions	11	5
Obsessionals	9	3
N.A.D.	5	—
Marital incompatibility	4	—
Manics	4	—
Alcoholics	4	2
	300	118

The positive findings are really of head complaints rather than of headaches, and I have included under head complaints all patients who mentioned their head in any way amongst their complaints.

Diagnosis.—In psychiatry clear-cut disease entities are the exception rather than the rule and it is often a matter of choice whether a patient is included under one diagnostic heading rather than another. The relatively high incidence of *depressions* may seem surprising. They are often missed and the correct diagnosis is of therapeutic importance because of the good response so many show to electrical convulsion therapy. All the cases included here showed a considerable degree of emotional disturbance; admission to hospital was recommended in 33 and "out-patient" E.C.T. in another 34. I tended to label patients *anxiety states* if they seemed to have a very definite load of symptoms or discomforts to carry, and *hysterics* if their complaints seem more definitely purposive and escapist, this often being associated with the type of personality that readily crumples up or runs away from difficulties. By *psychopaths* is meant in effect "sociopaths". About half of these cases had committed some offence and had been referred because of this; the remainder were grossly inadequate people. *Organ neuroses* included those referred for asthma, eczema and the like—and I must say that I have not had any more success than those who referred them to me. Under *organic reactions* are included the dementias (e.g. seniles) and toxic confusional conditions. This group is surprisingly small; but physical factors were of course of contributory importance in many others.

I saw proportionately more sexual problems and marital incompatibilities in private practice, and more hysterics and dullards in hospital practice. Otherwise the two groups were remarkably similar.

Severity.—Taking both groups combined, 82 of the 300 cases were recommended admission to hospital, 35 to mental hospitals and 47 to neurosis hospitals or neurosis centres.

Discussion.—It must be clearly understood that the figures in the table refer to head complaints rather than headaches. 118 of the 300 cases made some sort of head complaint, but only a very small minority had this as a main complaint; perhaps half a dozen of the private patients but, interestingly enough, two or three times that number of hospital patients. (This is possibly a reflection of the educational and intelligence differences of the two groups.) Head complaints were a good deal more common amongst women than amongst men, the relative frequency being about half as much again. Head complaints were not especially frequent in one group as compared with another, but it might be argued that there is a general association with conditions that are likely to have tension.

I believe that few of the patients who made head complaints had what might be called genuine headaches. What they had and were trying to describe was an unpleasant experience or emotion rather than a sensory experience. I think where one patient might say "My head aches" another might say "My head feels numb" and a third "I can't concentrate", and that these were different verbalizations of the same experiences; a very individual personal experience rather than a more objective experience of sensory pain. In brief, the patients I saw were trying to verbalize an emotional state rather than a sensory experience.

It is very likely that general practitioners get more complaints of headaches than do psychiatrists. They will certainly see far more organic headaches and they will probably refer doubtful cases to a general physician or neurologist rather than to us. I think it also probable that psychiatric patients go to them more frequently with the complaint of headache, as this is a respectable complaint to make. Moreover, many psychiatric patients fear or even desire to have some physical disease and hence they start off with a physical complaint. Further, I would venture to suggest that the complaint of many psychiatric patients is very considerably modified by the attitude, real or presumed, of the recipient of their complaints. If, instead of being asked what further complaints there may be, a patient is stopped and specially quizzed as soon as he mentions his head complaints, he will often be willing to elaborate on this theme owing to a mixture of motives such as gratification in the interest shown, fear, and so on. The danger of this is focusing upon what may be an unimportant and perhaps misleading facet of the total picture.

By the time, therefore, the "organic headaches" have been filtered off, or referred elsewhere, and patients have been reassured there is no physical disease, and they come to see a psychiatrist, they are probably more willing to verbalize in other and more correct ways what they feel wrong. How, for example, they cannot concentrate, or feel depressed, or cannot settle or make up their mind.

In confirmation of this I have often had patients referred to me with a doctor's letter saying that they had "functional" headaches who made no mention of such headaches at all when they came to see me but who, when asked specifically, have replied "Oh yes, I do have headaches too". And I have often asked patients who made head complaints whether these differed from the migraine from which they also may have suffered or from "hangover" headaches and, if reasonably intelligent people, they have usually assured me that they were quite different experiences.

The main point I wish to make is that when determining whether a head complaint is a manifestation of a psychiatric syndrome, it is important not to pull a patient up short as soon as he mentions his head and to quiz him on this, but to find out what other symptoms may be present as well. The possible significance of these other complaints involves the whole of psychiatry and cannot be gone into here; but suggestive points are (i) the proud proprietory attitude of certain neurotics to their headaches and (ii) the selective disturbance of function that is shown, i.e. the capacity to perform unpleasant tasks being particularly affected. On the other hand, persistent disturbance of function is not uncommon in depressions. A very difficult group are those with persistent headaches as a mono-symptomatic complaint. This often seems to occur in rigid obsessional hypochondriacs or in difficult bland hysterics.

I have not been concerned here with what I would regard as organic headaches precipitated by emotional factors. The studies of Wolff and others have demonstrated very clearly the importance of psychological factors and the personality background in the production of migraine, these emotional factors acting as a trigger that fire off a chain of organic events.

My main point is, therefore, that the head complaints that I meet and have been discussing are not headaches and I believe that had Keats been an ordinary out-patient he would not have started his ode with the statement "My heart aches"; he would have said "My head aches".

Dr. Denis Williams: Headaches are so common that they are accepted as part and parcel of life, and it is only when they become disabling or alarming that the patient seeks medical advice for them. Indeed, people who have never experienced a headache are so unusual that they have been investigated and the results of the investigations published.

Until recently work on headache has been mainly descriptive, and headaches have simply been divided upon the basis of the illnesses which have caused them. This was found to be very unprofitable, and Sir Edmund Spriggs said in his Croonian Lectures (1935, *Lancet* (ii), 1) that as he tried to relate headache to disease "The list grew and grew until it at last dawned upon me that I was making an inventory, not only of all diseases compatible with consciousness, but also of most of the other ills that flesh is heir to". He divided the causes of headache in 500 patients at Ruthin Castle as follows:

I.	Organic.—Intracranial disease	26
II.	Vascular	50
III.	Toxic.—Nephritis, allergy, endocrine, anæmia, alcohol, tobacco, drugs.. ..	71
IV.	Reflex and/or Toxic.—Rheumatic (spine muscles and joints) diseases of head, chest, and abdomen..	150
V.	Functional.—Migraine, asthenia, nervous exhaustion, neurasthenia, psychasthenia, mental	203
		500

This classification would not satisfy us now, but its very defects indicate the difficulty in compiling a list of this sort. Perhaps the most interesting feature of the list, even allowing for the obvious selection of Spriggs' cases, is that only 4% of them were found to have organic intracranial disease, for that is the first concern of the anxious patient with a headache.

Because of the impossibility of considering headaches in this way, I shall deal only with the structures responsible for and the mechanisms underlying the development of headache.

Headaches may arise through disturbance in structures. (1) Outside the cranium. (2) Inside the cranium.

There are however many disorders occurring elsewhere which cause headache by changing the state of intracranial structures. Obvious examples of this state of affairs are found in the intense headache of glandular fever or of typhoid fever, and in such toxic states as those following inoculation with T.A.B., or alcoholic excess. Whatever the prime cause, the headache arises in the local cranial structures, and a knowledge of the structures concerned greatly helps the understanding of the mechanism of headache.

The causes of headache.—(1) Local. Direct causes, e.g. sinus infection. (2) Local. Indirect causes, e.g. distortion of remote structures in the cranium by a cerebral tumour. (3) General causes—these (e.g. T.A.B. injection) cause headache through local mechanisms. (4) Psychological causes—many of these cause headache in exactly the same way as do general physical factors, the headache being "real" in the two states.

The anatomy of headaches.—The nerves responsible for the sensation of pain in the head are: The trigeminal, the glossopharyngeal, the vagus nerves, and the upper 3 cervical nerves. All the superficial and deep structures of the face including the teeth and sinuses are supplied by the trigeminal, the neck and ear having innervation from the upper three cervical.

The whole of the sensitive structures above the tentorium are supplied by the trigeminal nerve via its ophthalmic division, while those in the posterior fossa, including the undersurface of the tentorium, are innervated by the glossopharyngeal, vagus, and upper cervical nerves.

There is an important application of this innervation to clinical medicine, for it must be clear that if the pain-causing structure is supplied by the trigeminal nerve, whatever its position the pain will be felt in the trigeminal territory. Thus stimulation of pain-sensitive structures in the face, skull, anterior fossa, and middle fossa, including the whole of the upper surface of the tentorium, will cause pain in an area bounded behind by a line roughly joining over the ears over the vertex. This is true even if the cause is in the occipital lobe of the brain. Occipital pain must be caused by stimulation of structures in the posterior fossa or the cranium outside it, in the neck muscles, the cervical vertebræ and their joints or possibly behind the pharynx.

Sensitive structures.—Whereas virtually all structures outside the cranial cavity have a rich innervation and are sensitive to stimulation the reverse is true inside the cranium. The whole of the brain, the dura mater over the convexity, the ependyma, the bone and the diploic channels are insensitive to stimulation. Pain-producing structures are: (1) The basal and large cerebral arteries only. (2) The venous sinuses and the mouths of the veins as they enter them. (3) The dural nerves and some of the dural arteries. (4) The basal dura where it is adherent to bone.

The realization that full dilatation of the branches of the external carotid artery gives rise to intense migrainous headache, whilst dilatation of cerebral arteries by increase in the blood CO_2 content, is a daily occurrence unregarded by the subject, emphasizes the difference in behaviour and response of intra- and extra-cranial structures.

The physiology of headaches.—The results of stimulation of blood vessels and other structures inside and outside the cranium has been carefully studied by Dr. Harold Wolff of the Bellevue Hospital in New York, and we owe much of our present precise knowledge to his team of workers. I do not wish here to deal with the results of stimulation of such structures as teeth or sinuses, nor can I include a discussion of what is known of the physiology of migraine. Wolff has shown that the only subjective effect of stimulation of intracranial structures is pain, and that no other form of sensation is appreciated, nor is accurate localization of the pain-producing structure possible. The nearest we can get is that pain felt in front of a line joining the ears arises in the territory of the trigeminal nerve, that I have outlined, and that pain behind the line is felt mainly through the ninth and tenth cranial and first three cervical nerves. Pain may arise in intracranial structures through (1) Traction—e.g. veins, basal arteries and the dura. (2) Distension—e.g. arteries with a histamine headache. (3) Displacement—e.g. sinuses.

These causes may coexist as in the traction and displacement that occurs with a cerebral tumour. They may be produced in structures remote from the causal lesion, so that a cerebellar tumour, by interrupting the flow of cerebrospinal fluid, will cause internal hydrocephalus, and this, by traction on the veins entering the sagittal sinus, will cause a severe headache over the eyes, the occiput being pain-free. Not only do local lesions cause headache in this way but distant and general causes must use these mechanisms too. The general headache which follows T.A.B. injection can be explained on the basis of arterial hypotonia and consequent distension, and that of malignant hypertension through cerebral œdema and high intracranial pressure. It is a reasonable conclusion that general systemic causes of headache operate through a disturbance in the relationship of pressures inside and outside the cranial and cerebral vessels, producing distension and traction of the vessel. This is so in migraine, in anæmia, and in histamine headache. This is also the case in the reverse condition that exists after lumbar puncture or in dehydration. It is clear that although there are multiple causes for headaches few mechanisms or structures are finally involved in the production of the pain.

It is only when special local causes operate that the character and the site of the headache have specific diagnostic value. But even then the fact that so many and diverse causes must operate through so few final paths explains the diagnostic anonymity of headache.

I would like in closing to invoke the mechanisms I have described to explain the most common headaches of all, the headaches of neuroses. We know the differences between the frontal and occipital headache of a tense, anxious patient and the dull, vertical, throbbing pain of a depressive. In these conditions headaches are so usual and so stereotyped that they must have a physical basis. Wolff's work has shown that headaches are caused by muscle tension in the frontalis and occipital muscles and also in the cervical muscles. The headache in an anxiety state may be abolished by Novocain block of the motor nerves to the cervical muscles. It seems that this character is the symptom arising in the anxious and tense patient through continuous contraction of muscles attached to the cranium. This is not so in the depressive.

I do not think that this has yet been explained but I would like to suggest that events will show that it is vascular in origin, related to the hypotension, asthenia, and tendency to syncope that so many of these patients experience.

I have attempted to show that there is a known basis for every headache, however complex and obscure may be the process of its development.

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Section of Odontology

President—Sir WILLIAM KELSEY FRY, C.B.E., M.C., M.D.S.Durh., F.D.S., M.R.C.S.

[*February* 26, 1951]

Fibrous Dysplasia of Bone and Comparable Conditions in the Jaws

By FRANK L. INGRAM, D.M.R.D., L.D.S., M.R.C.S., L.R.C.P.

FIBROUS dysplasia of bone has been known under a variety of names and in the jaws it is still commonly called focal osteitis fibrosa. The lesion is not inflammatory but then neither is osteitis deformans or Paget's disease. Other names which have been used particularly for maxillary lesions are fibro-osseous dysplasia, fibrosis of bone (Elmslie, 1931), chronic hyperplasia (Davis, 1941), hyperostosis, fibrous osteoma, osteo-fibroma and ossifying fibroma (Eden, 1939), though perhaps some of these are separate entities. Localized fibrocystic disease is a name given to lesions occurring in a long bone which are probably either simple bone cysts or monostotic fibrous dysplasia. Radiologically these two may be very similar and indistinguishable without surgical intervention.

The other lesions to be considered and compared are Paget's disease, hyperparathyroidism or generalized fibrocystic disease—one of the two widespread diseases bearing the name of von Recklinghausen—and some localized lesions which are not usually confusing. These are central osteoclastoma, dental cyst and perhaps adamantinoma.

Fibrous Dysplasia of Bone

Fibrous dysplasia of bone as usually reported is polyostotic in distribution but it occurs in varying degrees of severity (Lichtenstein, 1938, and with Jaffe, 1942; McCune and Bruch, 1937). In the most severe form many bones are affected though the involvement is often predominantly unilateral. These rare cases are relatively often reported and with their widespread bone changes there occur patchy hyperpigmentation of the skin and endocrine upsets. In less severe afflictions one limb is chiefly involved and the upper end of the femur or humerus is a common site. The pelvis may be involved and the tibia or the forearm bones and quite frequently some of the ribs. There may be marked deformity of these bones with or without fracture, especially if the lesion is extensive and appears in childhood. The calvarium or any bone in the body may less often be affected.

When one of the jaws is the site of fibrous dysplasia, in the great majority of cases, the lesion appears to be monostotic. It is possible with all solitary lesions that other bones have changes which are too slight to be noticed. The typical lesion in the maxilla is quite different radiologically from the partially cyst-like lesion which occurs in long bones. There is enlargement of part of one side of the jaw and the bone pattern is much finer than that of normal alveolar bone. The jaw is denser to X-rays, partly because it is thickened but partly because the bone is reorganized on a different pattern. The trabeculæ are finer and the spaces between them smaller than normal. The margins of the lesions are indistinct with a slow transition to normal bone but occasionally the median maxillary suture appears sharply to limit the lesion.

Clinically these cases present as painless hard enlargements of the upper jaw of long standing. Just occasionally a dull ache is complained of but the lesion then is often presenting in the second or third decade when it is more likely to be active. Frequently the thickened bone is an incidental finding, the patient having failed to notice the slowly developed swelling. The lesion probably arises during the growing period of life and most of the enlargement occurs at this time, for the first five years

or so after onset. It does continue to grow slowly, however, in many cases after normal bone growth has ceased.

Fig. 1 shows some intra-oral films giving the typical appearance of a maxillary lesion in a man of 43. There is enlargement of the alveolar process, particularly in the molar region with the fine even pattern merging into normal bone in the canine region. The normal lamina dura is replaced by a much finer layer but the dark line of the periodontal membrane is still represented. The antral floor is displaced upwards in the molar region indicating encroachment of the bony mass in this direction. The swelling of the jaw was of the size of a small plum and was found on routine examination. The patient had not observed it. Two drill biopsies were taken from the lesion and the report was that the material was composed of irregular trabeculæ of well-formed lamellar bone in a fibrous tissue stroma with little osteoclastic activity. Probably the period of activity of this lesion was well past and the initially formed woven bone had been replaced by lamellar bone in the ensuing quiescent period. Enlargement of the right maxilla was also shown in the 20 degrees P.A. view of the jaws, the suboccipito-nasal projection.

FIG. 1.

FIG. 2.

FIG. 3.

Fig. 2 is a standard upper occlusal view of a woman of 31 who had had a swelling since childhood and had facial bone operations at the ages of 9 and 12. She presented with an acute abscess on the lateral incisor root. The pattern is finer than in the first case giving more the appearance of ground glass.

Fig. 3 is the view for the antra of this patient, the 45 degrees P.A. or occipitomental projection. It shows considerable enlargement of the maxilla both forwards and laterally with obliteration of the antrum. The head was tilted more than 45 degrees and there is more distortion than in the correct projection.

Fig. 4 shows a left maxillary lesion in a woman of 61. The pattern is typical though coarser than in the other two and ends sharply at the median suture.

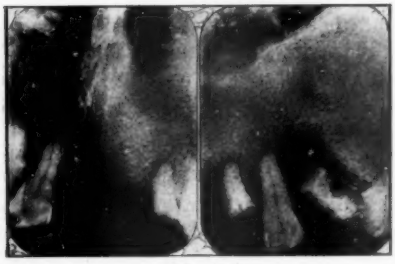

FIG. 4.

Fig. 5 is an oblique lateral view showing a circumscribed mass in the right maxilla of a woman of 40. Fourteen years later the lesion appeared practically unchanged and the antral view, Fig. 6, shows its discrete upper border with half of the antrum appearing normal above it. Because of its more discrete round form this lesion might be claimed to be an ossified fibroma but in intra-oral views its margin with normal bone was not sharply defined.

Fig. 7 shows a similar lesion in the mandible of a boy of 16. The whole thickness of the bone is composed of the typical fine pattern with loss of the distinction between cortex and medulla, just apparent in the premolar region in the occlusal. This even patterned lesion is uncommon in the mandible which is less often afflicted with fibrous dysplasia than is the maxilla.

FIG. 5.

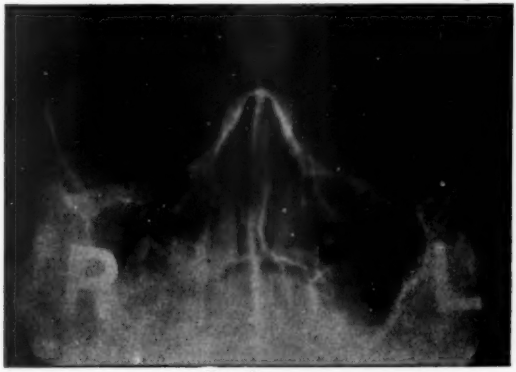

FIG. 6.

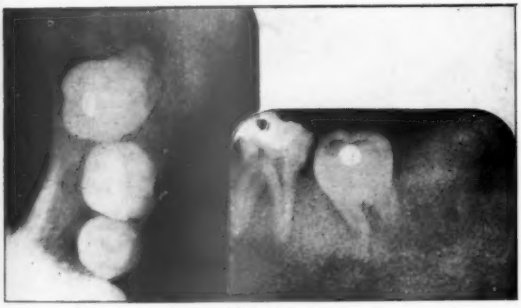

FIG. 7.

Fig. 8 is of a lower occlusal film of a woman of 41 who had first attended with this

FIG. 8.

FIG. 9.

lesion some fifteen years before. It is fairly circumscribed, ending at the symphysis, but its pattern is irregular with sclerotic zones and rarefied patches. There is gross local enlargement with something approaching a cortex formed at most edges of the lesion. It might be another ossified fibroma but such a diagnosis needs histological confirmation.

Fig. 9 shows one of two lesions in the mandible with partially circumscribed borders. This one is composed of a dense mass of bone fading off smoothly into normal bone anteriorly. Distally and inferiorly there is a transition to a rarefied zone, itself limited by a sharp white line. The occlusal view showed how circumscribed was the lesion and perhaps this also is an ossifying fibroma. On the other side of the mandible was a similar though less dense lesion and I prefer to consider them all as examples of fibrous dysplasia of bone.

Fig. 10 shows a dense mass of bone in the right maxilla of a man of 36. Two teeth have been deflected and their eruption obstructed by it, and though its margin is sharp it merges with normal bone with no trace of a soft tissue layer or lamina dura to suggest that it is composed of dental tissue. The premolar roots have been eroded and the canine is deflected back to the second molar region.

In Fig. 11 is a similar though more diffuse lesion in the mandible of a girl of 13½. There is a dense cloud of bone filling much of the medullary space almost to the lower border of the jaw and extending from the canine to the second molar region. There was no expansion except locally over the crowns of the displaced premolars. Three years later the second premolar had come to lie behind the second molar and the dense bone had extended backwards to envelop the growing third molar.

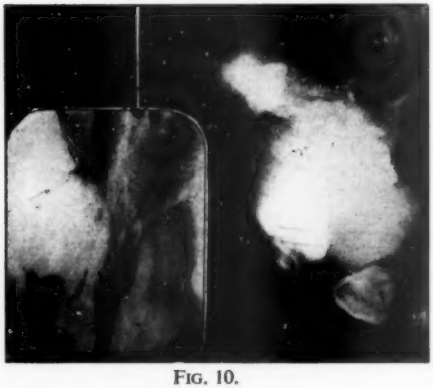

FIG. 10.

FIG. 11.

There is no evidence that any fibrous tissue has formed in the bone in these cases and perhaps they might be called central osteomata but they seem to me to be comparable to the other lesions, developing over the same period of time, occupying part of a bone and merging into the normal surrounding shadows.

Fig. 12 shows an occlusal film of a woman of 37 whose case was described by Rushton (1950). She had had a portion of her maxilla removed twelve years before and the report of the section was "fibrous osteitis". The anterior part of her mandible had been enlarging for about nine years and the section showed replacement of bone and marrow by fibrous tissue undergoing mucinous degeneration and enclosed in a shell of bone. In one place anteriorly the bone was absent and the lesion showed fluctuation though most of the pattern is not really cystic. It is composed chiefly of coarse strands of bone, rather reminiscent of the appearance of an osteoclastoma. There were no trabeculæ of bone or osteoid formed in the substance of this lesion as

FIG. 12.

FIG. 14.

FIG. 13.

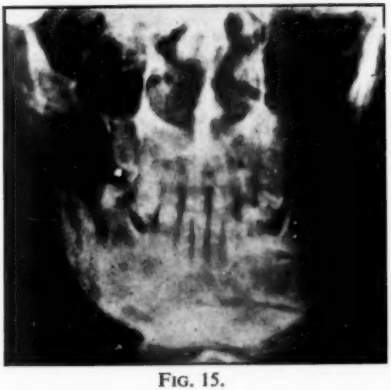

FIG. 15.

is usual in fibrous dysplasia. She also had bone changes in two of her long bones though these were not typical of the condition.

For comparison Fig. 13 shows an osteoclastoma in a girl of 9. The lesion has an ill-defined inner margin with a thicker and less sharp outer wall than has a dental cyst in an occlusal projection. The faint strands of bone to be seen are not in the substance of the lesion but represent ridges remaining in the wall after the intervening bone has been eroded away.

A similar appearance in a girl of 17 but with much fainter strands of bone proved to represent another example of fibro-osseous dysplasia. The section showed mature trabeculæ undergoing absorption internally and covered with osteoid externally. Deeper tissues consisted of spindle cells in a collagenous stroma containing many small osteoid trabeculæ, some showing partial calcification.

Figs. 14 and 15 are of a man of 32 with thickening of the right frontal region and of the right ramus and side of the mandible. His right eye was depressed and his right supra-orbital ridge was low and prominent. The pattern of the mandibular lesion is fairly homogeneous and the cortex and medulla are merged though there are many sclerotic patches and rarefied spaces in the grossly thickened frontal bone.

This is an example of two bones showing changes of fibrous dysplasia and the left side of the mandible and the other skull bones are normal in pattern and size.

Paget's Disease

Several writers have noticed points of similarity between the lesions in the jaws of fibro-osseous dysplasia and Paget's disease. Davis (1941) reported 3 cases originally presenting as focal osteitis fibrosa which developed the bone changes of leontiasis ossea due to Paget's disease many years later. Mr. Davis very kindly showed me many of his cases at the Ferens Institute and the final radiographs were certainly those of Paget's disease.

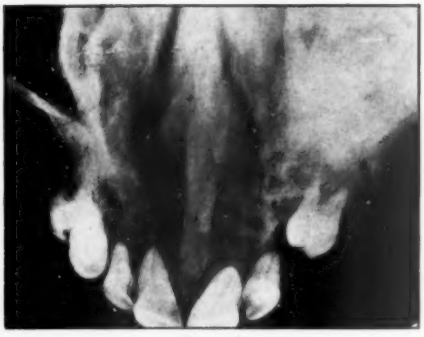

FIG. 16.

FIG. 18.

FIG. 17.

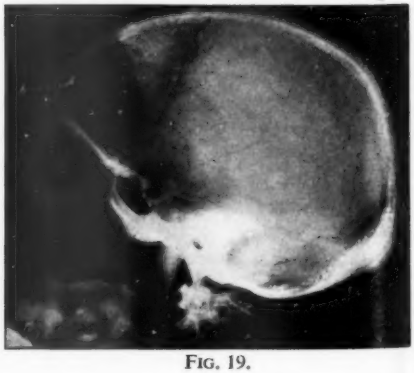

FIG. 19.

Fig. 16 is an occlusal film of a woman of 50 who complained of a tingling sensation of the left upper jaw for the previous year. There is enlargement of the left side of her maxilla but the pattern of the whole jaw is abnormal. The bone is generally porotic and of very fine pattern. The left side is thickened and mottled in pattern and the lamina dura of all the teeth is much slighter than normal. There is no normal bone pattern anywhere although the enlargement is only on the left.

Her cranium, Fig. 17, shows osteoporosis circumscripta, an early stage of Paget's disease. The normal fragment of cranium, high in the frontal region which is denser than the surrounding rarefied bone, decreased in extent steadily over three years of observation.

In Fig. 18, films of a woman of 68 show dense sclerotic patches in the left side of the maxilla and a fine bone pattern with marked porosis in the lower jaw which extended all round the mandible. The whole upper alveolar ridge was enlarged.

The anterior part of her cranium, Fig. 19, shows classical osteoporosis circumscripta.

FIG. 20.

FIG. 21.

Fig. 20 is an off-centred occlusal projection of another man but it shows well the dense masses of sclerosed bone or cementum which occur frequently round standing teeth. The right zygoma is enlarged as well as the maxilla and the cranium and base of skull also had changes of Paget's disease.

Fig. 21 shows part of the enormous upper jaw of a woman of 49 who had had a maxillary enlargement treated with X-ray therapy some thirteen years before. The lesion was apparently thought to be osteitis fibrosa but it seems likely that it was Paget's disease starting with enlargement of one side of the maxilla. X-ray therapy would be unlikely to affect either disease. Her maxilla now is grossly enlarged with a fine pattern, dense bone on either side and more rarefied and mottled bone anteriorly.

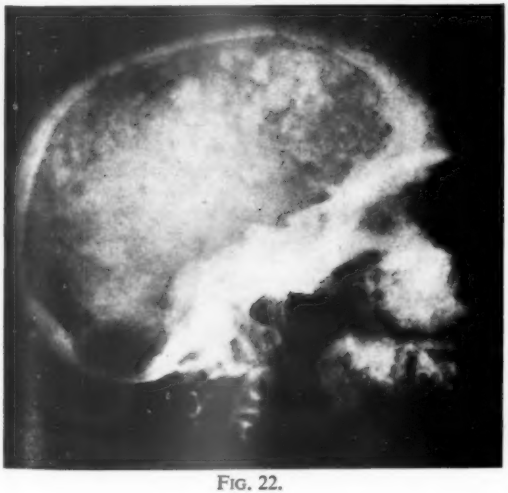

FIG. 22.

Both zygomata were enlarged, her cranium showed early changes and she presented as an example of leontiasis ossea due to Paget's disease.

Fig. 22 is a lateral view of the skull of a woman of 77 with advanced Paget's disease of the cranium, maxilla, zygomata and base of skull. She was deaf due to involvement of her middle ears and was clinically a classical example of leontiasis.

Fig. 23 is an oblique lateral view of the mandible of a woman of 57 in whom all the other bones appeared normal. It was grossly enlarged from the neck of one condyle to the

FIG. 23.

neck of the other and its pattern is very like that of the spongy form of Paget's disease in long bones plus the sclerotic patches which occur in the alveolar bone. Paget's disease may be localized to one bone for a long time but it is very uncommon for one of the jaws to be involved without some part of the skull.

Generalized Osteitis Fibrosa.

Fig. 24 is of an oblique extra-oral of a man of 24. The whole bone is severely porotic and its pattern is amorphous with complete replacement of the cortex and the lamina dura of the

FIG. 24.

FIG. 25.

tooth sockets and with only a faint shadow of the mandibular canal. The normal bone pattern is completely gone although the periodontal membrane is still represented (Fig. 25). He had had a fracture of one radius through a cyst-like lesion and it transpired that there were similar changes in the upper ends of his left humerus and right femur. All bones were severely rarefied and one lumbar vertebra had collapsed. The primary condition was chronic glomerulo-nephritis and he died of renal insufficiency shortly after these films were taken. His blood urea was 580 mg. per 100 ml. then, having risen steadily from 177 mg. three years before. He had developed a secondary parathyroid hypertrophy and one gland was ten times the normal size. His serum calcium varied between 7·75 and 10·3 mg. per 100 ml., and his serum phosphates between 5·3 and 8·8 mg. per 100 ml. These bone changes are those of severe generalized osteitis fibrosa or hyperparathyroidism, though general bone changes may be very slight or even absent with diagnostic biochemical changes when they are due to a parathyroid tumour.

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Section of Experimental Medicine and Therapeutics

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[*February* 13, 1951]

RECENT EXPERIMENTAL WORK WITH DEXTRAN AND DERIVATIVES

[*Abstract*]

Background to Biological Studies with Dextran

By Professor J. R. Squire, M.D., F.R.C.P., *University of Birmingham*

The following papers describe "work in progress". They are intended to illustrate the kind of information which can be obtained by studying quantitatively the behaviour in the body of a macromolecule such as the polysaccharide dextran[1]. Dextran solution as a resuscitating fluid for the prevention and treatment of shock is now familiar in many hospitals. Its value in this connexion is not under discussion here; its effectiveness, at least when manufactured to a close specification, is clear, though no doubt certain limitations will become more apparent with increasing experience. During 1948 we collaborated in the clinical trials of dextran (Bull *et al.*, 1949) and certain facts claimed our attention: the urinary excretion of a proportion of the dextran (the smaller molecules only): its slow removal from the plasma especially into the reticulo-endothelial system and lymph glands: and a tendency for erythrocytes to aggregate in the presence of dextran (the effect being greater in higher concentrations and more marked with material greater than 100,000 in molecular weight). The potential usefulness of such a macromolecule in experimental pathology became clear. Dextran can be prepared in a wide range of molecular size with similar chemical properties; it is electrically neutral, metabolically inert (no mammalian tissue extract is known to break it down), apparently non-toxic in high concentration, and can be estimated accurately after simple acid hydrolysis to glucose.

Some examples of fundamental problems which can be studied with dextran can be given.

(1) *The measurement of membrane permeabilities.*—The rate at which dextran molecules pass through a membrane can define permeability of many kinds of capillary, healthy and diseased. Filtration through the capillaries of the placenta, choroid plexus, ciliary body, joint-membranes and especially the renal glomerulus can be studied in this way, with a view to finding out the exact changes produced by various disease processes.

(2) *The reticulo-endothelial system* in normal animals is being studied, mainly by Dr. Maycock. Again, human studies in reticuloses and other diseases are called for.

(3) *Nature of antigen-antibody reactions.*—Dextran acts as a haptene toward the sera from animals immunized with *Leuconostoc* and certain other organisms. Dr. P. G. H. Gell has shown that the optimal proportion of dextran and antisera varies with molecular size.

(4) *Cell surfaces* differ in their behaviour from one another and with different macromolecules. For example, dextran, which causes marked erythrocyte aggregation, does not cause leucocytes to clump. Surface adsorption may be the mechanism of macromolecule removal by the reticulo-endothelial system, but this remains to be proved.

(5) *Blood-clotting mechanisms* depend upon charged molecules and are unaffected by dextran. Dextran derivatives such as the sulphate are highly charged, interacting and interfering with part of the reaction-chain involved in normal clotting. Again molecular size has been shown to be critical in determining the nature of these interactions.

From each of these pure research problems, useful clinical tests or remedies are likely to develop. As yet, only a start has been made in finding precise answers. Dextran preparations so far available, suffer from the defect of being somewhat disperse in molecular size, even when carefully prepared as "narrow cuts". We have been fortunate in our collaboration with Dr. and Mrs. C. Ricketts who have prepared fine fractions and derivatives, and suggested the further investigation of dextran sulphate previously described by Swedish workers. For membrane studies the high degree of asymmetry of the dextran molecule (of great advantage for investigating erythrocyte aggregation) makes

[1] We wish to acknowledge the numerous gifts of dextran preparations by Messrs. Dextran Limited.

interpretation somewhat difficult. We are left guessing as to whether the elongated molecule is likely to penetrate a membrane "pore" end-on, or sideways-on. Again, our chemical collaborators give promise of other series of polysaccharides—some even more elongated, others thought to be nearly spherical in molecular shape—which may assist in the solution of this kind of problem.

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Chemistry of Dextran and its Derivatives

By C. R. RICKETTS, Ph.D.

Medical Research Council Burns Unit, Birmingham Accident Hospital

DEXTRAN is a polysaccharide formed during the growth of a coccus, *Leuconostoc mesenterioides*, on a medium containing sucrose. The normal habitat of the organism is rotting vegetable matter in which its growth was observed by Pasteur (1861). During its growth, the organism produces an exo-cellular enzyme which polymerizes the glucose portion of the sucrose in the medium (Hehre, 1948) to form dextran. The fructose portion of sucrose is set free. Growth in a medium containing 20% sucrose results in conversion of about one-third of the available glucose to dextran.

Chemically, dextran differs from similar polysaccharides such as glycogen in that its glucose units are joined together through —1 : 6 glucoside links. The main chain of glucose units so formed has short branches at frequent intervals which are probably joined through —1 : 4 glucoside links (Stacey and Swift, 1948). The dextrans produced by various strains of *Leuconostoc* differ in the extent of their branching (Jeanes and Wilham, 1950). In their native state, the dextran chains are composed of about 200,000 glucose units, corresponding to a molecular weight of about 40 million. Such molecules are comparable in size with viruses.

Dextran has been widely used as a substitute for blood plasma in transfusions. For this purpose, the enormous natural molecules are quite unsuitable. Reduction in their size is effected by partial hydrolysis. Thereafter, a fractionation process allows gradation of molecular sizes and makes possible the selection of a sample containing the desired distribution of molecular size. Following the initial hydrolysis, the hydrolysate contains dextran molecules the largest of which are probably of molecular weight about one million and the smallest of molecular weight about ten thousand. This mixture is then submitted to fractional precipitation. When alcohol or acetone is added to such a solution and the temperature is slowly lowered, the larger molecules are precipitated first. This procedure allows the separation of a series of fractions (Ingelman and Halling, 1949; Ricketts, Lorenz and Maycock, 1950). Each such fraction is more homogeneous than the mixture from which it is derived but every fraction still contains a range of molecular weights.

Estimation of molecular weight.—The molecular weight of a polydisperse colloid may be expressed as a weight-average and as a number-average. Simple physical methods can be used to get an approximation to these averages for any dextran preparation but their more precise determination is more difficult. The viscosity of a dextran solution, measured by timing the flow through an Ostwald viscometer allows the derivation of the intrinsic viscosity of the dextran by calculation. Ingelman and Halling (1949) have determined the relationship between intrinsic viscosity and molecular weight (the latter being calculated from ultracentrifuge measurements) for one kind of dextran. The osmotic pressure of a solution is proportional to the number-average molecular weight. To supplement the figures obtained by measurements of viscosity, osmotic pressure measurements have also been made using collodion membranes of the type described by Adair (1949) and this work is still in progress.

On the whole, the available evidence indicates that dextran molecules are longer and thinner than proteins of comparable molecular weights.

Dextran fractions for experimental use.—The dextrans used for the experiments subsequently to be described, varied in size from larger than fibrinogen to very much smaller than albumin. Fractions composed predominantly of molecules of the fibrinogen size were used to investigate the factors affecting the erythrocyte sedimentation rate. Fractions composed largely of molecules smaller than albumin were used to estimate the limits of permeability of the glomerular membrane.

Dextran sulphate.—This compound is an ester of sulphuric acid with dextran prepared by treating dextran with chlorosulphonic acid and pyridine. The free dextran sulphuric acid so obtained is only stable in solution but solid sodium, calcium and other salts can readily be prepared. These compounds display an anticoagulant action like that of heparin, which is itself the sulphuric ester of a polysaccharide composed of glucuronic acid and glucosamine. The anticoagulant activity of sulphated polysaccharides has long been known

but previous compounds have always proved too toxic for clinical use. In the sulphation reaction the sulphate groups can enter one, two or all three of the hydroxyl groups in each glucose unit of the dextran molecule, the size of which may be varied from a few thousand to a few million. Thus it has been possible to prepare a series of compounds with very diverse properties but all having a fundamental structural similarity to heparin. These compounds have been used to investigate the mechanism of toxicity of sulphated polysaccharides and have led to the development of a material with therapeutic potentialities.

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Use of Dextran to Study Erythrocyte Sedimentation

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THE erythrocyte sedimentation is of proved clinical value, but numerous attempts to provide a chemical basis for this empirical test have been at best only partially successful. The work now briefly reported which has a similar aim has fallen into three stages:

(i) The development of an accurate technique eliminating known variables such as erythrocyte concentration, temperature, and also factors due to viscosity and specific gravity.

(ii) The formulation of the relationships between erythrocyte sedimentation and concentration of macromolecules of various sizes, using dextran.

(iii) The application of these data to erythrocyte sedimentation in plasma and serum of patients suffering from various diseases.

Method.—This has been previously described (Hardwicke, Ricketts and Squire, 1950). 30% cell concentrations were observed in vertical Wintrobe tubes at 25° C., and the maximum rate of fall (V_{max}) obtained from graphs based on frequent readings. This V_{max} was then corrected by conversion to a standard difference in specific gravity between erythrocytes and suspending fluid, and to a standard viscosity of suspending fluid, giving "a corrected V_{max}" (V_{mc}).

Results of adding dextran or other macromolecules.—As reported (Hardwicke, Ricketts and Squire, 1950), the increase in erythrocyte sedimentation was greater in higher concentrations and with larger molecular sizes of dextran. The relation between V_{mc} and concentration for a given macromolecule (or a given mixture of macromolecules) was found empirically to be linear on a double logarithmic scale (Fig. 1); this linearity was confirmed statistically. The equation which fits these results is:

$$\log V_{mc} = n \log C + \log K \qquad (1)$$

$$\text{or } \sqrt[n]{V_{mc}} = kC \qquad (2)$$

where n = slope of the line,

C = concentration of macromolecule in grammes %,

K is a constant equal to V_{mc} at 1% concentration of macromolecule

and k is similarly constant ($= \sqrt[n]{K}$)

The slopes (n) of the lines are clearly similar, no significant difference from the average value, 2·15, being found (Table I). The position of the lines, as defined by K, varies with the macromolecule employed.

TABLE I*

Substance	Concentration range	No. of observations	Regression (n)	Log K (y when log x = 0)	k
Dextran B ..	0·170–0·565 gramme %	32	2·147 ± 0·072	2·61 ± 0·038	16·6
Fibrinogen ..	0·158–0·752 gramme %	10	2·197 ± 0·113	2·29 ± 0·073	11·6
Dextran C ..	0·170–0·700 gramme %	8	2·046 ± 0·156	2·19 ± 0·170	10·4
Dextran D ..	0·382–1·360 grammes %	8	2·406 ± 0·190	1·63 ± 0·037	5·8

*Modified from Hardwicke, Ricketts and Squire (1950) *Nature*, **166**, 988.

[1]In receipt of a grant from the Medical Research Council.

Formula (2), page 559, is most useful for mixtures of macromolecules, e.g. A and B, since as confirmed experimentally,

$$^{2\cdot15}\sqrt{V_{mc(A+B)}} = k_A C_A + k_B C_B \qquad (3)$$

If the erythrocyte sedimentation can be determined for one of these macromolecules (e.g. B) alone, then

$$^{2\cdot15}\sqrt{V_{mc(A+B)}} - {}^{2\cdot15}\sqrt{V_{mcB}} = k_A C_A \qquad (4)$$

Clinical studies.—Formula (4) has been used in studying clinical material. We have confirmed that erythrocyte sedimentation depends partially upon fibrinogen concentration, partially upon a serum factor. The erythrocyte sedimentation has been measured separately in plasma (oxalated blood) and in serum (defibrinated blood). Suitable quantities of blood, obtained by venepuncture, were added to balanced oxalate (Heller and Paul, 1934), the remainder of the specimen being defibrinated with a bent glass rod and filtered through glass wool. 30% cell concentrations were prepared from part of both of these blood samples by dilution with appropriate amounts of plasma or serum. Fibrinogen concentrations in the plasma samples were determined as clottable nitrogen (Peters and Van Slyke, 1932).

Using formula (4)

$$^{2\cdot15}\sqrt{V_{mc\ plasma}} - {}^{2\cdot15}\sqrt{V_{mc\ serum}} = k_{fib} C_{fib}$$

(where k_{fib} and C_{fib} are the constant and concentration respectively for fibrinogen).

Fig. 2 shows the results obtained in 24 duplicate determinations on 20 blood samples from normal or diseased individuals. The patients were suffering from a variety of diseases

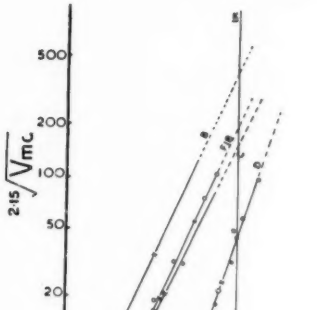

FIG. 1.

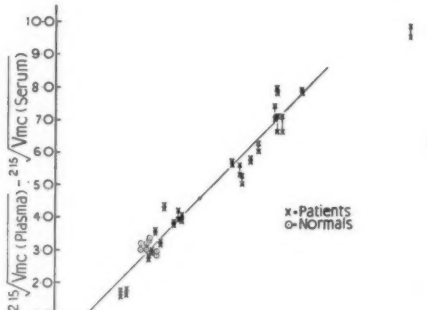

FIG. 2.

FIG. 1.—Effect of macromolecules on the sedimentation rate. B, C, and D are dextrans of Mol. Wt. 700,000, 220,000 and 120,000 respectively. Fib. = Fibrinogen. Experimental points drawn in for Dextran D and Fibrinogen. (Modified from Hardwicke, Ricketts and Squire (1950) *Nature*, **166**, 988.)

FIG. 2.—Relation between plasma fibrinogen and erythrocyte sedimentation.

including acute infection, chronic infection, neoplasm, reticulosis, nephritis or nephrotic syndrome, and showed wide variations in serum albumin and globulin concentrations. The close relationship shown between fibrinogen levels and the expression derived from this standardized erythrocyte sedimentation is apparent from the line in Fig. 2, and is confirmed by statistical analysis. (The case shown with 1·1% fibrinogen was suffering from obstructive jaundice; it was not included in the analysis since the V_{max} was over 200 mm./hour which value appears to be too close to the limiting velocity of fall for these relationships to hold.)

Discussion.—The use of $^{2\cdot15}\sqrt{V_{mc}}$, derived from experiments with added macromolecules (particularly dextran), is evidently applicable to the quantitative evaluation of one of the components responsible for raising the sedimentation rate in disease, namely fibrinogen. Since the $^{2\cdot15}\sqrt{V_{mc\ serum}}$ is used in assessing fibrinogen effect, the serum factor (or factors) presumably also follows similar relationships and the concentration must be proportional to the $^{2\cdot15}\sqrt{V_{mc\ serum}}$. Some examples of the variations in the two factors are given in Table II.

TABLE II.—VARIATIONS IN FIBRINOGEN AND SERUM FACTOR IN SELECTED EXAMPLES OF DISEASE

Diagnosis	Fibrinogen (grammes %)	Serum factor (fibrinogen equivalents)
Normal range (5 subjects)	0·28–0·32	0·11–0·29
Subacute bacterial endocarditis	0·37	0·51
Pulmonary tuberculosis	0·57	0·47
Nephrotic syndrome	0·76	0·81
Nephritis	0·60	0·21
Carcinoma of bronchus	0·68	0·46
Carcinoma of head of pancreas	1·10	0·50
Infective hepatitis	0·29	0·52
Cirrhosis of liver	0·20	0·10

Results already obtained suggest that the separate determination of fibrinogen and serum factor concentrations, when compared with the ordinary methods of reporting erythrocyte sedimentation rates, is likely to give information of greater clinical value both in diagnosing and in following the progress of disease.

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Renal Clearances of Dextrans of Varying Molecular Weights

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THESE studies on the urinary excretion of fractions of dextran of different molecular weights were undertaken with two main objects in view. The first was to get some idea of the rate of urinary loss of dextran when used as a plasma substitute and the second to attempt by using dextrans of known molecular weight to measure the range of permeability of the glomerulus.

The excretion of three fractions of dextran has been studied in rabbits. The average molecular weights of the three fractions were 5,000–10,000, 25,000 and 38,000. Simultaneous creatinine clearances were performed and were taken as a measure of the glomerular filtration rate. From the glomerular filtration rate and the concentration of dextran in the plasma for each ten-minute period the amount of dextran in the volume of plasma filtered was calculated (G). This was plotted against the actual amount of dextran excreted in the urine per minute (U).

In any one fraction of dextran it is probable that the rate of passage across the glomerular membrane will bear a constant ratio to the rate of passage of creatinine and that the rate of passage for dextran will fall with increasing molecular weight. Therefore for any given fraction of dextran the graph should be a straight line even if some of the filtered dextran is reabsorbed by the tubules or some dextran excreted by the tubules, provided this occurs with a constant tubular mass. The slope of the line will depend on the rate of glomerular passage and the point of intercept on whether or not dextran is reabsorbed or excreted by the tubules.

The best fitting lines for the experimental data for each dextran fraction were calculated. The equations for these lines measure the slope and so the rate of glomerular passage and also indicate the amount of dextran reabsorbed or excreted (Fig. 1 and Table I).

TABLE I

Molecular weight of dextran	Rate of glomerular filtration % of creatinine	No. of clearance periods
38,000	6 ± 1·9	8
25,000	19 ± 5·4	8
5,000–10,000	100 ± 28	9

The equations are:

Fraction of molecular weight 5,000–10,000 .. $U = 1{\cdot}00G - 0{\cdot}9$
Fraction of molecular weight 25,000 .. .. $U = 0{\cdot}19G + 2{\cdot}27$
Fraction of molecular weight 38,000 .. .. $U = 0{\cdot}06G + 1{\cdot}95$

From these results it appears that dextran is mainly excreted by glomerular filtration. If any tubular excretion or reabsorption occurs it is relatively small in amount.

It can be calculated that, assuming a glomerular filtration rate of 120 ml. per min., it would require the infusion of 7·2 grammes per hour to maintain a plasma concentration of 2 grammes% of a dextran of 38,000 molecular weight. Such a dextran is, from the experimental results, filtered at about 5% the rate of creatinine. Assuming a plasma volume of 2·5 litres, then in 4·8 hours after stopping the infusion half the plasma dextran would be lost. The "half-life" of dextran fractions of molecular weights 25,000 and 7,000 would on a similar basis be 1·2 hours and 0·24 hour. Dextran of these molecular weights would be of little value for resuscitation of shocked patients.

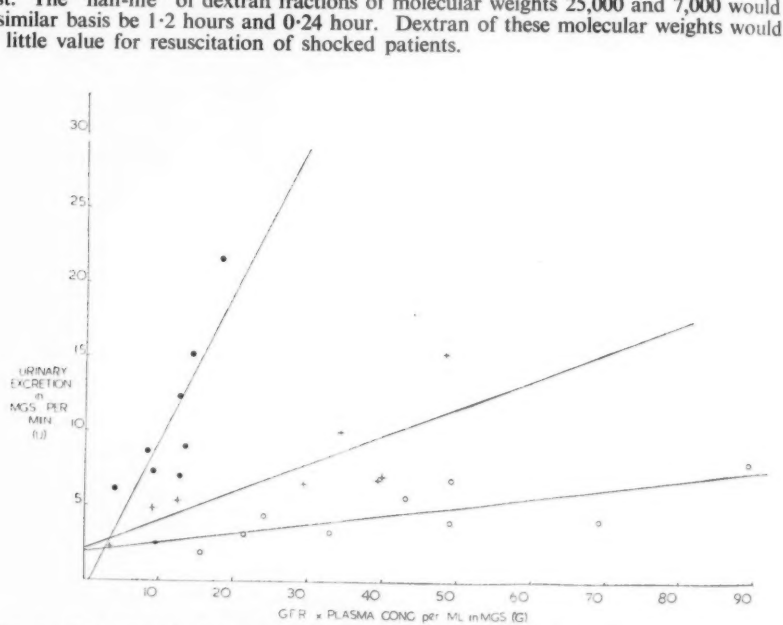

FIG. 1.—The amount of dextran (G) in the volume of plasma equivalent in volume to the glomerular filtrate (as measured by the creatinine clearance) has been calculated and plotted against the urinary excretion of dextran per minute (U). This graph shows the results for the three fractions studied, the fraction of molecular weight 5,000–10,000 by solid dots, that of 25,000 by crosses, and that of 38,000 by open circles.

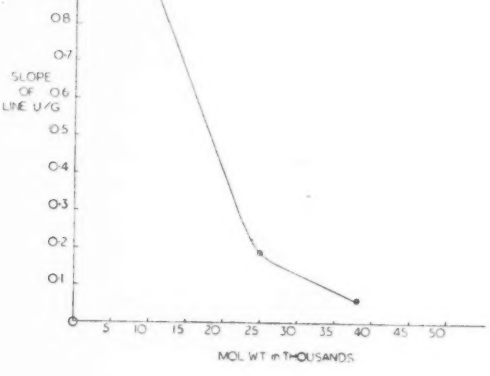

FIG. 2.—In this graph which indicates the range of glomerular permeability the slopes of the lines in Fig. 1 have been plotted against the molecular weights of the dextran fractions in thousands.

A striking feature of the results is the great effect of molecular size on the rate of movement of dextran across the glomerular membrane.

The membrane may be considered as a simple sieve membrane. All the "pores" of it are as permeable to creatinine, inulin, and glucose as they are to water and so all these substances pass across it at the same rate and their concentrations are the same on either side.

A small number of "pores" are known to be permeable to hæmoglobin so there must be a fall in the number of pores permeable to molecules in the range between these two sizes. As the number of pores available for filtration decreases with increase in molecular size, so the area available for filtration and the rate of filtration must fall.

The distribution of pore size will be indicated by the graph obtained by plotting the rate of filtration at the glomerulus as represented by the slope of the line U/G against molecular weight (Fig. 2). The results are preliminary but they indicate that all the pores are permeable to molecules of weight about 7,000, then there is a rapid fall to 20% permeable at 25,000 and a flattening out of the curve to 6% permeable to molecules about 38,000.

These results can only apply to dextran which has a markedly asymmetric molecule. Many factors such as molecular shape and charge and changes in glomerular dynamics, e.g. increased filtration fraction may well affect the movement of molecules across the glomerular membrane. We are looking forward to examining these possibilities and to attempting to estimate the range of pore size of the normal and diseased glomerulus in the human subject.

Experiments with Dextran Sulphate as an Anticoagulant

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BERGSTRÖM demonstrated in 1936 that the sulphuric esters of polysaccharides have a heparin-like anticoagulant activity. It was shown by Astrup *et al.* (1944, 1946) that certain of these compounds were unsuitable for clinical use because they precipitated fibrinogen, agglutinated platelets and caused death from internal bleeding with large dosages.

Gronwall, Ingelman and Mosimann (1945) synthesized three esters of dextrans of varying molecular weight and reported that these all showed toxic properties similar to those of other sulphonated polysaccharides, and concluded that molecular weight was not an important factor in determining the toxicity of these compounds. From the data later furnished by Ingelman (1947) it was possible to infer that his least toxic preparation was appreciably larger in molecular weight than heparin. Accordingly, a range of compounds extending in molecular weight both above and below those prepared by Ingelman was prepared and examined. It was found that when the starting-material (dextran) was below a certain critical molecular weight, the sulphuric ester prepared from it was free from the undesirable properties described above and no more toxic than heparin itself in experimental animals. This compound is shortly to be submitted to therapeutic trial.

Dextran sulphates.—From Table I it can be seen that the dextran sulphates of molecular weight 35,000 and above behaved differently from those of molecular weight 20,000 and less. The first group (hereafter called "large molecular weight" dextran sulphates) behaved similarly though in varying degree, in causing (1) Precipitation of fibrinogen, (2) Agglutination of platelets, (3) Deposition of granular material in reticulo-endothelial cells. The second group ("Small molecular weight" dextran sulphates) were free from these properties.

Large molecular weight dextran sulphates.—The toxicity of these compounds was found to be dependent upon their tendency to precipitate fibrinogen. When this occurred in plasma *in vitro* the platelets became adherent to, and entrained in the precipitate, forming clumps. This explained the thrombocytopenia and fibrinogenopenia which occurred *in*

TABLE I.—SHOWING VARIATION IN BIOLOGICAL PROPERTIES OF DEXTRAN SULPHATES WITH VARIATION OF MOLECULAR WEIGHT

Dextran sulphate serial No.	Approximate molecular weight	Fibrinogen precipitation	Platelet agglutination	Deposition in R.E. cells
D	367,000	+++	+++	+++
B	124,000	+++	+++	+++
A	114,000	++	++	+++
E	52,000	++	++	++
C	35,000	+	+	+
I-2	20,000	0	0	0
I-1	16,000	0	0	0
I-4	12,000	0	0	0

vivo in rats to whom the material was given intravenously. Subsequent phagocytosis of the particles of this precipitate accounted for the appearance of granular material in the reticulo-endothelial cells of the liver, spleen and bone-marrow of animals killed between one hour and twenty-eight days after the injection of large molecular weight dextran sulphate. Dextran sulphate, like heparin, gives a marked metachromatic reaction with toluidine blue *in vitro* and it was found that this granular material in the reticulo-endothelial cells gave a similarly conspicuous reaction when sections were stained with toluidine blue and examined.

These properties of the large molecular weight compounds made them obviously unsuitable for therapeutic use and from this standpoint they were discarded.

Small molecular weight dextran sulphates.—On the other hand, the small molecular weight dextran sulphates, like heparin, had no effect on platelets *in vivo* or *in vitro*, nor, when administered to experimental animals did they give rise to deposits in reticulo-endothelial cells. Their properties, in these respects, are contrasted with the large molecular weight compounds in Table I. One typical batch of this material when assayed against International Standard Heparin had an activity of 17–20 units/mg. It was found to be effective by parenteral injection only. The effect of intravenous administration of varying doses on the clotting time in rabbits is seen from Fig. 1.

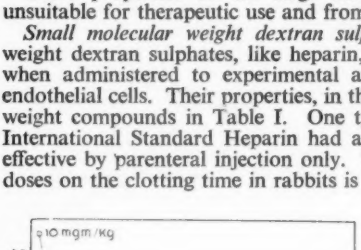

FIG. 1.—Showing the effect on the clotting-time of intravenous administration of increasing doses of "small molecular weight" dextran sulphate in the rabbit. Ordinate—Clotting time (minutes). Abscissa —Time after injection (minutes).

With dosages up to 500 mg./kg. body-weight, no toxic effects were observed in the mouse, rat, rabbit, dog or monkey. With certain batches transient reactions were observed in the guinea-pig but these did not prove fatal. Careful histological examination of the liver, spleen, kidneys, skeletal and heart muscle, skin, bone-marrow, lymph nodes, endocrines and central nervous system showed no parenchymal damage though this was looked for after single injections, repeated injections and over periods from one hour to three months after the last injection. Intravenous administration produced no effect on the blood pressure, pulse-rate or respiratory rate. At anticoagulant concentrations, a negligible effect was produced on the erythrocyte sedimentation rate, and since the material has no osmotic effect on the red cells, it was found that the ordinary hæmatological estimations were not interfered with. No effects were observed on the motility or phagocytic activity of white cells *in vitro* or *in vivo*. Attempts to produce allergic sensitivity to dextran sulphate were not successful.

Mode of action.—It seems probable that dextran sulphate owes its anticoagulant properties to the strong electro-negative charge upon its acidic groups, since, like heparin, its action is opposed by strongly basic substances such as protamine. For its action, dextran sulphate, like heparin, requires the presence of a co-factor in serum or plasma. In the presence of this co-factor its action is that of an antithrombin.

Summary and conclusion.—The sulphuric esters of dextrans of molecular weight less than 20,000 are free from the undesirable toxic effects of previously described sulphonated polysaccharides. One such compound is being submitted to clinical trials and, if found satisfactory, may serve as a synthetic analogue of heparin. It should be possible to produce this material at considerably lower cost than heparin.

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Section of Otology

President—D. F. A. NEILSON, F.R.C.S.

[*December* 1, 1950]

The Pathology and Surgical Treatment of Bell's Palsy

By TERENCE CAWTHORNE, F.R.C.S.

INTRODUCTION

MORE than a century and a quarter ago Sir Charles Bell (1821), Surgeon to the Middlesex Hospital and Principal of the Great Windmill Street School of Anatomy, drew attention to the distribution and function of the seventh cranial nerve. This he described as the respiratory nerve in order to emphasize what he considered to be its primary function.

For many years he had been trying to sort out the function of the different nerves supplying sensation and movement to the head and face, and in particular to distinguish between the function of the fifth and seventh cranial nerves. In a later book on the nervous system Bell (1844) collected together his principal communications to the Royal Society on his investigations into the facial and other nerves and illustrated these with a series of interesting and illuminating cases. Thus the name of Bell became attached to facial paralysis, and was used to describe all cases of isolated peripheral facial paralysis, no matter what the cause.

Nowadays, however, the term Bell's palsy is reserved for those cases of peripheral facial paralysis in which there is no obvious cause such as injury, infection or new growth; or in which there is nothing to suggest a more centrally placed lesion. Gowers (1893) regarded Bell's palsy as a definite disease group, and said:

"The features of these cases are so uniform, allowance being made for differences in degree, that we are justified in regarding the pathological condition as the same in all—a neuritis within the fallopian canal."

This group still accounts for the majority of cases of isolated peripheral facial paralysis as may be seen from Table I; this gives the causes in a consecutive series of 270 case of peripheral facial paralysis which I have seen in recent years. I have not included in this series any cases that were seen, or operated on, before the war, because of the difficulty in collecting full notes.

TABLE I.—CAUSES OF PERIPHERAL FACIAL PALSY

Bell's palsy	157	Herpes	13
Injury	55	New growth	9
Otitis media	30	Others	6

Thus the proportion of cases of Bell's palsy in this series is 58%, which is somewhat lower than has been reported by previous observers, possibly because of the large number of traumatic cases which have been seen.

PATHOLOGY

In the recent series of 157 cases of Bell's palsy on which this paper is based the sex and age incidence is as follows:

TABLE II.—SEX INCIDENCE OF BELL'S PALSY IN 157 CASES

Male	84
Female	73

TABLE III.—AGE INCIDENCE IN BELL'S PALSY IN 157 CASES

0–10	1	41–50	36
11–20	15	51–60	24
21–30	37	61–70	19
31–40	24	Over 70	1

Although idiopathic facial palsy is perhaps more frequently seen than any other nerve paralysis, our knowledge of its possible causes, and of the effect upon the nerve trunk, is meagre owing to the small amount of material available for detailed histological examination. It is generally believed that the majority of cases in this group are due to a lesion of the facial nerve trunk at or near the stylomastoid foramen where it emerges from the narrow bony fallopian canal in the temporal bone, and it is such cases that are included under the heading of Bell's palsy. It has been felt that swelling of the nerve trunk in this region, possibly as the result of exposure to cold, may, if it extends upwards into the narrow bony fallopian canal, result in severe compression and in consequence the ability to conduct impulses will be impaired or lost. It will of course be appreciated that peripheral facial paralysis due to other causes such as poliomyelitis, a virus infection, or a neurofibroma of the seventh nerve may sometimes be accidentally included under the heading of Bell's palsy.

Although there had never been any evidence of infection or swelling in the very few cases submitted to detailed histological examination, Ballance and Duel (1932) found that when they examined the nerve trunk in the living in severe and prolonged cases of paralysis submitted to a decompression operation the nerve trunk just above the stylomastoid foramen appeared, even to the naked eye, swollen. This appearance has since been recognized by many other observers.

The appearance of the nerve as seen with a binocular dissecting microscope giving ten diameters of magnification has also been described by myself, Cawthorne (1946), and is as follows: On opening the sheath of the nerve, which is found to consist of several layers, the outer layer being thick and the inner layers being very thin indeed, the nerve trunk when eventually exposed appears to be unduly constricted at the level of the stylomastoid foramen. There is a natural though slight narrowing here, but in cases of Bell's palsy the narrowing appears more obvious than normal, possibly because of the swelling of the nerve above this level. At and just above the site of the constriction there are to be seen as a rule one or more thin hæmorrhagic streaks running longitudinally upwards for about 2 mm. in the long axis of the nerve. Above the constriction the nerve itself swells out often beyond the confines of the sheath; and this swelling may extend upwards for 0·5 to 1 cm. before tapering off to its normal calibre. In this swollen segment there may be one or more pink-tinged patches.

In three cases of long-standing paralysis I found that the nerve trunk in this region was reduced to a shrunken and reddened strand that was adherent to the sheath. These appearances have been noted in 34 out of 37 cases recently operated upon, and in most of these the paralysis had been present for two months or more.

Now in experimental nerve injuries it has been shown by Weiss (1943) and by Denny-Brown and Brenner (1944*a*) that ischæmia resulting from compression is followed by swelling of the nerve trunk proximal to the lesion. Similar findings have also been noted clinically by Brain, Wright and Wilkinson (1947) in cases of median nerve palsy due to compression of the nerve in the carpal tunnel. Kettel (1947), in a detailed review of Bell's palsy, concluded: "Bell's palsy is a pathogenic entity, the primary and central feature being a disorder, a 'dysregulation' of the circulation, in most cases affecting only the nutrition of the nerve as the most susceptible tissue, from which an ischæmic paralysis arises."

He also noted in a proportion of his cases that the bone in the neighbourhood of the fallopian canal was softened and necrotic, and this he attributed also to ischæmia.

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Treatment

When it comes to treatment, consideration should always be given to the state of the nerve trunk at the probable site of the lesion. It has been the general custom to regard supportive measures for the paralysed facial musculature and electrical stimulation of these muscles by means of interrupted galvanism as treatment, and it is generally understood as being treatment of the lesion itself. It is, I think, important to realize that, valuable though these supportive measures may be, they are only able to keep the paralysed muscles in good condition. They contribute nothing whatever to the treatment or relief of the lesion responsible for the paralysis; and they will be of no help unless the physiological continuity of the nerve can be restored. Fortunately in the majority of cases this happens spontaneously, but in some there remains a varying degree of permanent residual paresis, whilst in a few there is never any recovery at all. In this connexion Pickerill (1945) remarked:

"It is said that 75% of cases of Bell's palsy recover spontaneously, and therein we think lies the cause of lifelong disfigurement for many people."

The figure generally given is that 80% get full spontaneous recovery, but in this series the figure is 50%. The figure for full spontaneous recovery would have been higher had I seen all cases of partial palsy.

In 151 cases the proportion showing recovery, partial recovery or no recovery within two months of the onset of the palsy are given in Table IV. I should add that where the palsy is complete and lasts for two months there is always some residual paresis. This may well be the reason for the use of the term Cynic Spasm in Græco-Roman medicine to describe the spasm that is not infrequently seen following severe Bell's palsy.

TABLE IV.—AMOUNT OF RECOVERY WITHIN TWO MONTHS OF ONSET OF PARALYSIS IN 151 CASES OF BELL'S PALSY

Full recovery ..	75	Partial recovery ..	19	No recovery ..	57

When confronted with a case of Bell's palsy it is important to try and assess the severity of the case and to estimate the prospect of spontaneous recovery.

Two valuable guides to the severity of the lesion are the extent of the paralysis and the ability of the nerve to transmit a faradic stimulus. The following table shows the relationship between these two factors and early spontaneous recovery in the cases which I have seen.

TABLE V.—RELATION OF DEGREE OF PARALYSIS AND ELECTRICAL CONDUCTIVITY TO SPONTANEOUS RECOVERY IN 151 CASES OF BELL'S PALSY

	Full recovery	Partial recovery	No recovery within two months
Paralysis incomplete. Faradic response normal ..	41	4	0
Paralysis complete. Faradic response normal ..	20	4	0
Paralysis complete. Faradic response reduced ..	14	8	0
Paralysis complete. Faradic response absent ..	0	3	57

It will be seen from the above table that complete spontaneous recovery is usual whenever the paralysis is partial or the nerve retains its ability to conduct a faradic response. On the other hand complete paralysis with absence of response to faradic stimulation indicates a severe lesion of the nerve and the probability of permanent residual paresis.

In a further observation, Gowers (1893) noted: "Indeed, whenever there is nerve degeneration and whenever the paralysis is complete for a month, some trace of it usually remains."

In this connexion it is interesting to note that Denny-Brown and Brenner (1944*b*), in their experimental study of pressure-induced nerve paralysis, describe an intermediate type of pressure lesion where there is paralysis with delayed recovery without degeneration in which the lesion lasts from one to nineteen days, possibly longer. My own experience has been that if spontaneous recovery is going to be complete it nearly always shows some sign of starting well within a month of the onset of the paralysis.

In the severe group, which has been estimated as amounting to 20% of all cases of Bell's palsy (including those which are not complete), Ballance and Duel (1932) advocated exposure of the nerve at the stylomastoid foramen and in the lower part of the bony fallopian canal and slitting up the sheath, thus relieving pressure on the swollen nerve. This they termed "Decompression", and for the first time the nerve was examined and directly treated at the site of the lesion. They claimed that this procedure ensured the maximum amount of final recovery and this claim has since been supported by many other observers.

The operation is safe, convalescence uneventful and quick, healing should be by first intention, and the small scar behind the ear need be the only relic of the operation.

I do not, however, wish in any way to imply that the operation should be undertaken lightly or without special experience. In nearly every case coming to operation the facial nerve trunk is intact. The surgeon must not do anything that will damage the nerve, which must be handled with the greatest care, and nothing must be done to hinder healing by first intention. I must confess that I still approach each one of these operations with some trepidation, and I am always relieved when the nerve has been exposed without being damaged; an incident that has not as yet happened at my hands. I am quite sure that this operation should not be lightly embarked upon, and it is just as necessary and, I may add, just as useful in this as in other operations on the temporal bone, to get into training for it by adequate practice on the cadaver.

Using a post-aural incision, the lower part of the mastoid process is opened until the sheath of the digastric groove is exposed. This is followed inwards until the shining sheath of the facial nerve at the stylomastoid foramen is exposed.

The opening of the nerve sheath and any manipulation of the nerve itself are best carried out in a magnified field, and for this operation I always use a binocular dissecting microscope giving ten diameters of magnification (Cawthorne, 1941); and I think that the microscope not only enables one to recognize pathological changes, but it also ensures gentle handling of the nerve. I believe that it is more important to use the microscope for the finer part of facial nerve surgery than for any other kind of surgery on the temporal bone. Before closing the wound of entry I always cover the exposed nerve with a thin sheet of prepared amniotic membrane. The wound is, of course, closed completely to encourage healing by first intention.

The very nature and duration of the lesion for which decompression is justified make complete recovery unlikely, but I have no doubt that in severe cases decompression ensures the maximum amount of recovery, and I think that it should always be considered whenever total paralysis has lasted for more than a month.

In the present state of our knowledge we cannot say with any degree of certainty within

Although there had never been any evidence of infection or swelling in the very few cases submitted to detailed histological examination, Ballance and Duel (1932) found that when they examined the nerve trunk in the living in severe and prolonged cases of paralysis submitted to a decompression operation the nerve trunk just above the stylomastoid foramen appeared, even to the naked eye, swollen. This appearance has since been recognized by many other observers.

The appearance of the nerve as seen with a binocular dissecting microscope giving ten diameters of magnification has also been described by myself, Cawthorne (1946), and is as follows: On opening the sheath of the nerve, which is found to consist of several layers, the outer layer being thick and the inner layers being very thin indeed, the nerve trunk when eventually exposed appears to be unduly constricted at the level of the stylomastoid foramen. There is a natural though slight narrowing here, but in cases of Bell's palsy the narrowing appears more obvious than normal, possibly because of the swelling of the nerve above this level. At and just above the site of the constriction there are to be seen as a rule one or more thin hæmorrhagic streaks running longitudinally upwards for about 2 mm. in the long axis of the nerve. Above the constriction the nerve itself swells out often beyond the confines of the sheath; and this swelling may extend upwards for 0·5 to 1 cm. before tapering off to its normal calibre. In this swollen segment there may be one or more pink-tinged patches.

In three cases of long-standing paralysis I found that the nerve trunk in this region was reduced to a shrunken and reddened strand that was adherent to the sheath. These appearances have been noted in 34 out of 37 cases recently operated upon, and in most of these the paralysis had been present for two months or more.

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In the present state of our knowledge we cannot say with any degree of certainty within

the first two to three weeks of the onset of the paralysis which cases are unlikely to recover completely and spontaneously. Those with only partial paralysis are almost certain to make a good recovery unaided and such cases, which may well form the bulk of the group of Bell's palsy, can be conscientiously given a good prognosis.

Where the paralysis is complete and when, after two weeks—for it takes this time for a dead nerve to lose its ability to transmit a faradic stimulus—there is no response to faradic stimulation, the likelihood of complete spontaneous recovery is very much reduced.

If at the end of a month the position is unchanged, then I think that the patient should be given the chance of having a decompression operation. A proportion of these will within six months or so show some degree of recovery even if left alone; but I am quite sure that in such cases an early decompression will lead to a more satisfactory recovery. An interesting and significant feature is that in most cases submitted to decompression there is some return of movement within a week of operation. This suggests that there are in the compressed nerve trunk some active neurones that are restored to normal activity when, and possibly only when, the pressure is relieved. Electromyography shows this, and I have observed patients in whom there was no faradic response but in whom the electromyograph indicated the presence of a few active motor units, and in whom no recovery of movement was seen until after decompression.

Finally, let us consider the results that are likely to follow decompression. It is, at the outset, important to appreciate that anyone who has sustained a complete facial paralysis lasting one month is unlikely to get complete recovery of all movements even with an operation. Some of these cases, possibly 50%, will eventually achieve some degree of spontaneous recovery. There will, however, be some residual paralysis or even spasm. I have found that decompression encourages a speedier and a more complete return of movement, and it is less likely to be complicated by spasm of the facial musculature, a condition that may cause almost as much distress as the original palsy.

Of the 37 cases that I have operated upon since noting this appearance of the nerve under the microscope in 1945, 31 have shown considerable improvement following decompression. The six unsuccessful cases included three in whom no changes could be found in the appearance of the nerve at operation, and I believe that these were not cases of Bell's palsy. The other three were those in which the nerve in the region of the stylomastoid foramen was reduced to a reddish streak adherent to the sheath. If I come across such another I think that I shall excise the shrunken segment and bridge the gap with a nerve graft.

With regard to supportive and other measures for the paralysed facial musculature, I favour a hook attached to a dental plate to support the drooping mouth. Gentle interrupted galvanism three or four times a week during the stage of complete paralysis helps to keep the muscles in good tone and encourages the patient. At the first sign of any return of voluntary movement I think that active exercises, in front of a glass, are most helpful. Velascus in the sixteenth century ordered those of his patients who were suffering from facial palsy to carry a trumpet, and he enjoined them to sound it frequently so as to give strength to the facial muscles. We can do the same with a tin whistle or a mouth organ.

In conclusion I would say that Bell's palsy is a condition in which the facial nerve just above the stylomastoid foramen is found to be altered in size and in colour, the result probably of local vascular changes. In severe cases early exposure of the nerve where it lies swollen and compressed in the lower part of the bony fallopian canal offers the best chance of good recovery of function. In the present state of our knowledge it seems advisable to wait at least a month before embarking upon an operation, but it may be that in the future we shall find a clue which will tell us at a much earlier date which cases are unlikely to recover spontaneously. If that be so, then the sooner the operation is done the better.

Lastly, I should like to express my gratitude to my colleagues at the National Hospital for Nervous Diseases, Queen Square, at King's College Hospital and elsewhere who have been kind enough to refer their cases to me.

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Air Commodore **E. D. D. Dickson** presented some results obtained by the non-operative treatment of Bell's palsy. Since September 1949 a total of 37 cases of facial palsy had been seen and received conservative treatment in the Department of Physical Medicine at the R.A.F. Central Medical Establishment. They were all suffering from a lower motor neurone lesion. Of the 37 cases all but 4 recovered, showing no sign of facial weakness. Of the 4 who did not make complete recovery one was an officer who had had no treatment since the onset of the condition fifteen months previously; a sling operation was declined by the patient. In the other 3, recovery was progressing slowly as shown by the myograph. Of the 37 patients, in only 3 was the condition due to trauma in some form: one following a fractured skull, another due to a blow on the occipital region, and the third following mastoidectomy.

The time of onset before being seen varied from a few days to several months but on the average it was eight to ten days after the onset of symptoms. As a routine in the R.A.F. they tried to centralize any cases they wanted to observe, and the patients were seen by a neurologist, an otologist, a dental officer, and the physical medicine department. The treatment consisted of anodal galvanism over the sternomastoid foramen, interrupted galvanism to the paralysed muscles, exercises in front of a mirror when voluntary movement had returned, and support of the paralysed muscles by a dental splint. The majority of patients were discharged from the department of physical medicine after about four weeks' full treatment. The patients on discharge still showed signs of recovery and were seen generally at monthly intervals. The cases were reviewed periodically. From the point of view of the time factor there was one particular case which stood out in his memory. The patient was a prisoner of war during the last war. He had a chronic otitis media whilst a prisoner and went through all the phases of giddiness, involving the labyrinth, and facial palsy, which last became complete. He was seen some eighteen months after the onset of his symptoms and underwent a radical mastoid operation. Advanced cholesteatoma was found eroding facial canal and labyrinth. He made a good recovery but his facial palsy remained. After nearly eight months of treatment and observation he was finally given a facial sling with tantalum wire and that afforded him adequate facial symmetry. He (Air Commodore Dickson) had followed up this man for two or three years and to his great amazement, about two years after the sling operation, he regained movement on that side of the face. It was evident therefore that the time of recovery was sometimes a little longer than the two months described.

The belief that many cases subjected to decompression would have recovered given the appropriate conservative treatment has been strengthened by a further experience in three cases. It had been decided to subject them to decompression but owing to some postponement of the operation, when seen at a later date, signs of beginning recovery as shown by voluntary movements at the angle of the mouth were observed.

Miss **Josephine Collier** said that she was glad that Mr. Cawthorne had referred to the various pathological conditions which might give rise to Bell's palsy. She was sure that it was a condition with a multiple ætiology. On the question of exposure to cold: Everyone had seen such cases but why was it not more common in cold weather or cold countries? Dr. Neill Hobhouse had referred to the number of cases he had seen in hot weather in Malta in the 1914–18 war, and others had made similar observations recently. Dr. F. M. R. Walshe, many years ago, had drawn attention to the epidemic feature—how cases turned up in small crops—and she could not see how this could be explained by arteriolar spasm giving rise to ischæmic neuritis. Mr. Cawthorne had mentioned facial paralysis due to herpes. She asked whether he had had complement fixation tests done in cases where no vesicles were discovered? She had known of zoster antibodies being found in such cases which meant that a virus infection, in at least some cases, was indistinguishable from simple Bell's palsy. While a virus infection would not act at the stylomastoid foramen, it would explain the epidemics.

It was necessary also to comment on the prevalence of Bell's palsy (so-called) during poliomyelitis epidemics. She had first noticed this in 1947 and at one time had under her care three children under 8 years with a clinical picture identical with Bell's palsy. In these, the cerebrospinal fluid was not examined but she had seen cases since with typical Bell's palsy and changes in the cerebrospinal fluid, and others had reported similar findings. She would like to know how Mr. Cawthorne had been able to exclude the possibility of a nuclear origin. Looking back on her pre-war cases she had found at least two that she submitted to decompression which must have been due to a nuclear lesion. Such textbook criteria as examination of taste and what the Americans call "tearing", i.e. alteration of lacrimal secretion, were seldom of practical value.

Problems of ætiology also arose because Bell's palsy was sometimes recurrent, sometimes familial, occasionally bilateral. The clinical group associated with hypertension suggested that some cases might be due to hæmorrhage in the fallopian canal analogous to the hæmo-

rrhage that may occur in the retinal or conjunctival arteries. These varieties raised doubts about the site of the lesion being always at the stylomastoid foramen.

On the question of prognosis, all would agree with Mr. Cawthorne that upwards of 80% of cases recovered spontaneously and completely within a few weeks, these being the cases which retained the response to faradism. Miss Collier thought that otologists had been hypnotized by Duel's statement that 85% of cases of Bell's palsy recovered early and completely with the implication that the remaining 15% did not recover without interference, but the real facts were not so easy. The 85%, or whatever the figure was, consisted of cases of simple physiological block, i.e. non-degenerative lesions. The remaining 15% were either degenerative or mixed lesions, i.e. with some nerve fibres degenerated and others in a state of physiological block. Now once degeneration had occurred (and definite evidence for this could not at present be detected until the third week after degeneration, when fibrillation might be found by electromyography) recovery could only take place by regeneration, a process that necessarily took time. Rates of regeneration varied but clinical evidence of reinnervation could not be expected before three months and might not appear for six to nine months.

Did Mr. Cawthorne decompress to prevent degeneration or with the intention of promoting regeneration? In either case, why did he pick on an arbitrary period like four to six weeks. Mr. Cawthorne had said that he relied on the faradic reaction. Did he do serial observations, or did he take a negative faradic response on one occasion, or even two, as evidence for degeneration? If so, how did he account for the rapid recoveries sometimes claimed? If he operated to prevent degeneration then he should do it during the stage of physiological block, i.e. within the first few days, before the faradic response had become negative, i.e. in every patient, which would mean including the 80% who would recover anyhow in a few weeks.

She said that it was necessary to separate the non-degenerative stage, which might perhaps be called the predegenerative stage, from the degenerative stage. If this were not done, no intelligible discussion was possible. Electromyography has shown that the so-called ischæmic block could persist, even as long as six weeks, perhaps longer. Maybe these were the cases of rapid recovery after decompression which would have recovered in any event.

There were three possibilities with Bell's palsy whether operative treatment was undertaken or not—recovery without degeneration, recovery by regeneration with the defects that follow degeneration, and failure of regeneration, i.e. permanent paralysis. Unfortunately there were no statistics giving the proportions in each group.

Once degeneration had occurred there was, as yet, no single test which would tell us about the possibility of spontaneous regeneration. It was well known that good functional recovery might be present while the electrical reactions—faradism and galvanism—were still abnormal. Her conversion from belief in decompression for every case of Bell's palsy with a negative faradic response dated from some dramatic experiences ten years ago when 2 patients with the reaction of degeneration under an anæsthetic showed rapid clinical recovery while waiting two to three weeks for operation. If she had operated earlier she would certainly have claimed, and have received, the credit for the good result. Nowadays they could get evidence of impending reinnervation from serial observations of the strength duration curve and from electromyography. These might give a favourable prognosis between three weeks and three months before facial movement could be seen. Miss Collier read a quotation from Erb's own work on muscle testing by electrical reactions written in 1876:

"He who believes that for the purpose of an exact diagnosis of a paralysis, a single examination, however careful, is sufficient, will frequently be liable to error, since electrical investigation in many cases affords no very valuable information, and it is only in certain forms of paralysis that its results are free from ambiguity and permit perfectly definite inferences to be drawn; whilst in all cases positive conclusions can only be arrived at by comparing the condition of electrical excitability with all other clinical symptoms."

In the matter of the appearance of the nerve on decompression she would have liked to have known the relation between the operative findings and the length of time after onset of the paralysis. Did Mr. Cawthorne find the swelling he had mentioned and the hæmorrhagic streaks equally marked early and late? It was difficult to see why the swelling described should be limited to the lower part of the descending course. She had not operated on any case of Bell's palsy since she had had an operating microscope, so had no evidence. Did Mr. Cawthorne think that the hæmorrhagic streaks were evidence of thrombosis? If so, it would be worth while doing biopsies of the sheath. She knew from operating in traumatic cases that the nerve completely filled the canal in life and, of course, nerve bundles in any nerve always bulged out when the nerve sheath was opened. The difficulty was to have a standard for comparison and in this connexion her anatomical colleagues were beginning some investigations on the blood supply of the facial nerve. The normal blood supply from the stylomastoid artery was, of course, longitudinal. She would like to know how far up the

shrinkage extended in the cases where the nerve was reduced to a thin strand. She could not understand how such a condition could be limited to the site of the stylomastoid foramen. She agreed with Mr. Cawthorne that a completely scarred segment should be excised and grafted. Did he think the constriction he finds is an exaggeration of a normal constriction? If so, it was curious that the nerve should be pathologically constricted just where the fallopian canal was widest.

Miss Collier agreed with Air Commodore Dickson as to the value of physiotherapy in the treatment of Bell's palsy. When Bell's palsy resulted in degeneration of the nerve and denervation of the muscles recovery was bound to take time whatever the treatment given to the nerve. Since denervation always meant wasting something should be done to limit this. The residual disfigurement after regeneration was due to wasting and to mass movements and spasm—these latter being brought about by branching of the regenerating axons—an inevitable anatomical result of regeneration.

Miss Collier said in conclusion that she considered that there might be a place for decompression in Bell's palsy, but she doubted whether they had yet found it. They might find progressive changes giving intense motor unit irritability in the early stages which would be detectable only by electromyography, or daily measurement of electrical reactions by the strength duration curves might reveal that a physiological block was progressing towards degeneration, a degeneration which might be prevented by early decompression. Until some work on these lines had been done there was a need in this field for those recently distinguished or castigated by Lord Moran as uneasy agnostics.

Dr. Ruth Bowden mentioned that the material which she had brought for inspection at the meeting was actually obtained by examination of nerve injuries in the limbs and not in the face, but they had no evidence that the facial nerve differed in its physiological behaviour from any other nerve supplying voluntary muscles. She had been very much interested to hear Mr. Cawthorne comment on the electrical reactions and their value in the diagnosis and prognosis. Although faradic and galvanic tests had proved most valuable, and indeed would continue to be valuable, there were some refinements of testing which seemed to offer clearer details of the changes occurring in the nerve.

To study the excitability of a tissue it was necessary to know the strength and duration of the effective stimuli, but neither of these could be measured successfully when faradic and galvanic tests were used. The results shown to the Section were obtained with a constant current stimulator designed by Dr. P. Bauwens. The technique of testing was standardized as far as possible and serial examinations were made by a single observer. On each occasion a comparable healthy muscle was examined in addition to the paralysed muscles, as deviations from the normal during denervation and reinnervation were informative.

One of the objects of electrodiagnosis was to obtain evidence of the presence or absence of wallerian degeneration in the nerve trunk at the earliest opportunity after the onset of injury or disease. It was important to stimulate the main nerve trunk as well as the muscle itself. When nerve fibres had been completely interrupted by damage or disease, stimulation of the nerve trunk was ineffective if it was applied above the level of the lesion. However, during the first two or even three days after infliction of the damage it was possible to elicit a contraction in the appropriate muscles by stimulating the nerve trunk below the lesion but the strength of stimulus required rose. By the third or fourth day nerve conduction failed below the lesion and there was clear evidence of a degenerative lesion of the nerve fibres. (It was of course impossible to show by electrodiagnosis whether the supporting tissues of the nerve trunk were in continuity or divided.) Within the first two or three days after a degenerative injury the results of stimulation of the muscle belly might show no significant differences from the comparable healthy muscles. There was a gradual rise in the threshold of effective stimuli of short duration, and the response to stimuli of 1/1,000 sec. duration might fail by about two to three weeks after injury (cf. R.D. using Faradism and Galvanism). For a variable period, the responses to the longer duration stimuli were rather more easily elicited and the contraction of the muscle changed in character and became sluggish. In some cases where there had been a complete degenerative lesion in the nerve trunk, a feeble response to short duration stimuli might be obtained from the muscle belly. The threshold was greatly raised in comparison with the healthy muscle. In 9 out of 82 cases of complete degenerative injuries a response to short duration stimuli was obtained at an abnormally high threshold. At first it seemed possible that a few motor nerve fibres had been spared, although the results of nerve stimulation suggested that this was unlikely. In such cases electromyography was of value for it provided a delicate method of detecting the presence of a few intact motor nerve fibres. Definite evidence of degeneration of the nerve fibres could not be obtained by electromyography alone for two or even four weeks.

If the lesion of the nerve produced a block to conduction of the nerve impulses, studies

of the electrical reactions of the nerve trunk and muscles were also of considerable value in diagnosis and prognosis. Stimulation of the nerve trunk above the site of the block failed to elicit a contraction in the appropriate muscles; whilst stimulation below the level of the lesion resulted in a brisk contraction which was obtained throughout the period of paralysis which might last for as long as ten to twelve weeks. The reaction of the muscles to stimulation in cases of block to conduction of nerve impulses apparently varied according to the degree to which degenerative changes had occurred in the nerve trunk. In clinical work an uncomplicated block was not often found, and there might be degeneration of some of the nerve fibres. The significance of some of the observations made in cases of mixed block and degeneration of nerve fibres was not yet understood.

However, it was safe to state, that taken in conjunction with the complete clinical picture, the serial testing of electrical reactions (by a standardized technique in which the strength and duration of the stimulus could be measured) was an aid to diagnosis, prognosis and treatment of nerve injuries.

Mr. I. A. Tumarkin said that he had studied this same problem some twenty years ago. He had investigated 150 cases (*Proc. R. Soc. Med.*, 1936, **29**, 1685) and his conclusions were diametrically opposed to those of Mr. Cawthorne. He was quite convinced that when facial palsy failed to recover, the lesion was in the geniculate ganglion. At that time he had drawn attention to the syndrome of crocodile tears, i.e. spasmodic lacrimation associated with mastication. This syndrome was evidence of a lesion involving the great superficial petrosal nerve thus proving that the strangulation had occurred at the geniculate ganglion and not peripherally as Mr. Cawthorne believed. He had found the syndrome in many cases which had failed to recover and it was noteworthy that one of Mr. Cawthorne's own patients had the same condition. It was difficult to see how decompression of the descending portion of the facial nerve as recommended by Mr. Cawthorne could cure a patient whose lesion was in the geniculate ganglion.

Nevertheless, as Mr. Cawthorne had shown, and as he himself had found in 1934, a limited operation on the mastoid itself apparently benefited certain cases, despite the paradox that the lesion was central to the site of operation. In 1936 he had suggested that the improvement might be attributable to the removal of bone and the resulting vascular decompression which presumably would relieve the pressure on the strangulated nerve. He had therefore come to the conclusion that the tedious decompression of the nerve could be abandoned in favour of an extensive cortical exenteration of the mastoid process. He had, however, pointed out that no operation whatsoever was justifiable once the nerve had died. In such cases, the nerve sheath was still intact and perfectly protected within the fallopian canal—thus presenting an ideal route for new axons pushing out. Decompression at that stage would do no good and might do harm. Vascular decompression, in his opinion, was the operation of choice but could only be of value in the early stages when the nerve was viable. Clearly, since 80% of cases recovered spontaneously it was unjustifiable to operate on all patients. Some criterion was required to distinguish those cases which were not going to recover spontaneously. He had found in following up his patients that when the onset of the palsy had been accompanied by marked pain and loss of taste the prognosis was much worse than when the onset had been symptomless. The electrical reactions gave no help whatsoever at that time but it seemed possible that the newer methods of electromyography might yield the desired criterion. However, in the absence of any such criterion and in view of the indifferent results of delayed operation, he had come to the same conclusion as Air Commodore Dickson, namely that it was best to rely on non-operative measures.

Mr. Cawthorne said that he had been greatly interested by the results obtained in Air Commodore Dickson's series of cases. There was not time to answer all the points raised by Miss Collier. He had not done complement-fixation tests on any of these cases. Bell's palsy indeed, as two speakers had said, might cover a multitude of palsies, and he had taken every care to include under the heading of Bell's palsy only those cases for which no other possible cause could be demonstrated. Most of his cases had been operated upon between two and three months after the onset of the palsy. A longer time had elapsed between onset of palsy and operation in the three cases in which the nerve was shrunken.

As for the faradic response, he quite agreed with Miss Collier that it was of the utmost value to do serial faradic responses, repeating them, despite the overworked condition of the physiotherapy department, and he wished Dr. F. Cooksey had been present to give his experience of these cases at King's College Hospital.

Section of Dermatology

President—W. N. GOLDSMITH, M.D., F.R.C.P.

[*January* 18, 1951]

Progressive Symmetrical Sclerodermia with Sclerodermatous Nodules.—R. H. SEVILLE, M.D., M.R.C.P., for F. R. BETTLEY, M.D., F.R.C.P.

F. P., male, aged 68.

History.—The condition started as a pinkish-white swelling over the metacarpophalangeal joints two and a half years ago and spread slowly to the fingers, the backs of the hands and then the forearms. For the past two years the fingers and wrists have been stiff and very susceptible to cold ("dead fingers"); tightness of the face and coldness of the feet have been noticed during the last year.

Five months ago small nodules developed in front of the right shoulder and spread to the anterior part of the chest, the shoulders, the upper arms and to a less extent the neck and abdominal wall. More recently the skin has felt stiff over the lower abdomen.

For the past month there has been slight muscle fatigue in the legs.

There have been no symptoms suggestive of systemic involvement. Apart from recurrent sore throats, "industrial dermatitis" on the hands and later on the body and legs, attributed to printers' ink seven years ago, and the death of the patient's wife three years ago, the history does not contain any relevant information.

FIG. 1.—Nodular sclerodermia.

Examination.—Many ivory-coloured nodules of firm consistency measuring 3–10 mm. in diameter are present in the areas mentioned (Fig. 1). Some are elongated and tend to lie along the skin creases. The surrounding skin over the shoulders is normal; that over the chest front has an ivory colour and shows minimal infiltration in contrast to the areas of ivory brown thickening over the lower abdomen. Similar smooth areas of ivory brown induration are seen on the backs of the hands and forearms, thighs, calves and to a less extent the face. The skin of the fingers is pink and adherent to the underlying tissues. There is some reduction in the power of the fingers and movement is limited in the wrist, neck, and to a less extent the face, where there is some loss of expression. Over the ears the skin is shiny but not infiltrated.

There are two areas of violaceous fibrosis on the buccal mucous membrane of the right cheek. Apart from an infected left lower molar, no abnormalities were detected in the general physical examination.

Special investigations.—X-ray chest: No calcification was seen in the skin nodules; no abnormalities were detected in the lung fields or cardiac outline. Barium swallow showed no abnormalities. (Dr. W. Smith.)

Biopsy (right shoulder): Section shows that the nodule is composed of a fibromatous type of collagen exhibiting massive hypertrophic bundles crossing in different directions and containing many spindle-shaped nuclei. There is homogenization of collagen and perivascular round-cell infiltration typical of sclerodermia (Fig. 2). Similar changes are seen in a section of skin from the forearm. (Dr. H. Haber.)

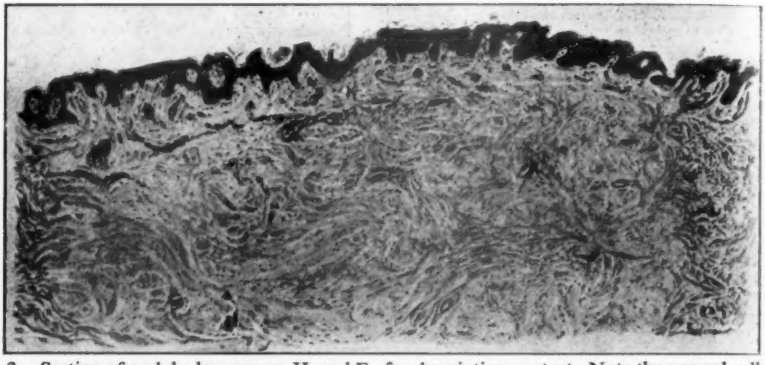

FIG. 2.—Section of nodule, low power, H. and E., for description *see* text. Note the normal collagen at both ends of the section. (Drawn by Miss A. Gretener.)

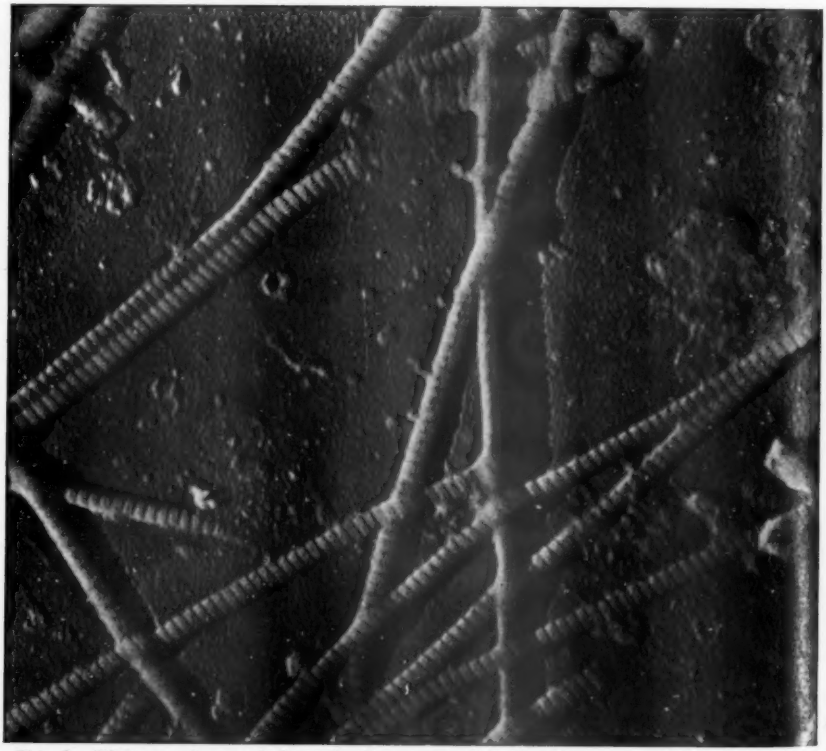

FIG. 3.—Electron micrograph from the lower part of a sclerodermatous nodule. Approximate magnification × 26,000. For description *see* text. Note the presence of amorphous material and the apparent disintegration of the ends of the collagen fibrils.

Comment.—The patient is presented because of the apparent rarity of nodular sclerodermia. Thomas Addison probably reported the first case in 1854 when describing "True Keloid".

I have appended a bibliography of other similar cases.

POSTSCRIPT.—A specimen of tissue from one of the sclerodermatous nodules was submitted to the Department of Biomolecular Structure, Leeds University, for electron micrographic examination. The provisional report stated that there was incipient degeneration of collagen fibrils in the nodule; these changes were more marked in the lower part of the nodule, where there was also a tendency to incipient degradation (Fig. 3).—R. H. S.

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Dr. F. Parkes Weber: Has this nodular type of sclerodermia been found in any cases as a precursor of the diffused type? I am not quite sure from the history of this case whether nodules were present in the terminal parts of the upper extremities before the symmetrical sclerodactylia developed.

Dr. Seville, in reply: Nodular sclerodermia has occurred as a precursor of diffuse sclerodermia in half of the published cases I have found (*see* Bibliography). In the three cases of localized sclerodermia, the nodules were invariably preceded by other manifestations of sclerodermia.

Case for Diagnosis ? Granuloma Annulare.—HAROLD WILSON, M.R.C.P.

D. A., aged 30. Married. Gardener.

History.—Eighteen months ago the present condition began as small, solid, itching spots which he referred to as sun blisters. These were first noticed at the back of the neck, later they appeared at the sides of the scalp, on the forehead and the right forearm.

Past history.—Scarlet fever in infancy. Otherwise nothing relevant.

Family history.—Father alive and well. Mother alive; suffers from rheumatism. 1 sister alive and well. Wife and 1 child alive and well.

On examination.—The eruption consists of small annular yellowish lesions which heal with slight superficial atrophy, not sufficiently deep to produce baldness. On the neck and scalp these lesions are very numerous. On the forearm they are more discrete.

Investigations.—Blood count: R.B.C. 4,800,000; Hb 105% = 15·0 grammes%; W.B.C. 10,000. Neutros. stab 3%, segmented 31%, lymphos. 59%, eosinos. 2%, basos. 1%, large monos. 4%. W.R. negative. Mantoux 1 : 1,000 ++. X-rays of chest and phalanges revealed nothing abnormal. Urine, no porphyrins detected.

Reactions to light.—Infra-red, radiant heat, visible light—normal reaction as far as can be ascertained.

Carbon arc: Normal M.E.D: 2 mins. 47 secs. at 30 ins. Patient's M.E.D. 1 min. at 30 ins.
Kromayer lamp: Normal M.E.D.: 12 secs. at 2 ins. Patient's M.E.D.: 6 secs. at 2 ins.
Kromayer lamp and Wood's filter: Normal reaction.
Kromayer lamp using blue Uviol lens: Normal M.E.D. produced in 60 secs. at contact. Patient's M.E.D. produced in 20 secs. at contact.

Comment.—The possibilities suggested by the clinical appearance of the lesions were granuloma annulare or sarcoid, or it could be regarded as an unusual type of reaction to light. There is no doubt that its distribution might well have been determined by exposure. I particularly noticed his scalp; he keeps his hair very well cut and the lesions on the side of the scalp where the hair is short present almost as a reticulum. Higher over the scalp the eruption fades out, and on the other side it begins again. His right forearm, he keeps

bare because he is a gardener and he has to bed out plants and so on, and the eruption has faded out on the under-arm. He also works in a greenhouse, the glass being normal window glass. We tested him against light and he gives an abnormal reaction, between 3,000 to 3,600 Ångstrom units, his erythema dose being one-third to one-half that of a normal subject. I think that is a pathological result as he has dark hair. Moreover, I noticed to-day that the erythema produced a fortnight ago has not gone down. I feel that possibly light has something to do with determining its distribution although I should not like to say that it has caused the condition. I have not seen anything like this described as being the result of light, although a sarcoid-like type of light eruption has been described by Andrews, G. C. (1950, *Arch. Derm. Syph., Chicago*, **62**, 26).

Dr. H. Haber: This is a very interesting case from the histological point of view. The epidermis shows thinning due to an infiltrate which lies immediately under the epidermis and occupies the first third of the corium. At close inspection the infiltrate consists of round cells, a few histiocytes and numerous giant cells, both of the foreign body and Langhans type. The interesting feature is the peculiar change of the collagen which exhibits actinic degeneration combined with necrobiotic changes. In some places the necrobiotic change provides clearly a focus round which histiocytes and giant cells are arranged. In one such focus a few polymorphs with degenerated nuclei could be demonstrated. The difficulty in the interpretation of the histologic findings lies in the merging of both types of degenerated collagen. But on close analysis one can clearly distinguish the change as seen in granuloma annulare. The diagnosis therefore suggested is that of granuloma annulare in a very unusual situation.

Dr. G. B. Dowling: I do not think that lupus can be excluded either clinically or histologically. I have had under my care for years a case of widely disseminated lupus in which many of the lesions are ringed and very similar in appearance to those present in this case. Histologically the lesions in this case appeared to me to be tuberculoid.

Dr. R. D. Sweet: I have been treating an almost identical case whose lesion started on the forehead and has progressed downwards. I called it annular sarcoid. Suddenly the patient came out with a series of miliary lesions on both forearms. I did not take a biopsy from the original lesion but later took one from a miliary lesion and it showed the appearances of sarcoidosis. I gave her enormous doses of calciferol, and whether that is the reason I do not know, but all the lesions are now regressing very rapidly.

Dr. L. Forman: Is this a case of non-diabetic necrobiosis? The histology showed large areas of altered collagen surrounded by foreign-body giant cells. I would like to know whether the patient has an altered blood sugar tolerance curve.

POSTSCRIPT (June 1951).—Some months ago, this patient developed a shower of miliary lesions on both arms. The histological appearances of these strongly suggested granuloma annulare. No tubercle bacilli were found in sections from a fresh lesion and guinea-pig inoculation was negative. His glucose tolerance test was within normal limits.—H. W.

Hypertrichosis Lanuginosa, Acquired Type.—A. LYELL, M.D., and C. H. WHITTLE, M.D., F.R.C.P.

Mrs. A. S., aged 35.

In September 1950 an excessive growth of hair developed suddenly on the face, neck and upper part of the body. Four months previously she had had a cystectomy for carcinoma of the bladder. (Histological specimen shown.)

The new hair is pale and fine and grows over the whole of the face including the nose, and over the neck, arms and shoulders (Figs. 1 and 2). Since she has been under observation this lanugo hair has grown longer and thicker and has spread farther down the trunk, but the legs are free at present.

The terminal hair and the nails are normal; the pubic hair is of the female distribution. There is no family history of any abnormality of the hair. Menstruation was normal until the start of œstrogen therapy (5 mg. of stilbœstrol daily) on December 12. No improvement has followed this treatment. The blood pressure is normal (140/80 mm.Hg). The excretion of urinary 17-ketosteroids was 9·3 mg. *per diem* on November 29.

Comment.—The abnormality known as hypertrichosis lanuginosa is extremely rare. According to Cockayne it is congenital, and is inherited as a dominant characteristic. The plate in Kaposi's Atlas shows a young girl with this peculiarity. The lanugo hair covers the face and chest, and the nose is also hairy; also her scalp hair is lanuginous. The preceding plate is of her father, whose appearance is even more forbidding.

In our case the hair peculiarity has been acquired recently, and the picture of hypertrichosis lanuginosa has been grafted upon her entirely normal hair growth and features. Her dark scalp hair and eyebrows contrast strangely with the blonde fluff which covers her face and neck.

Ormsby showed a case of a comparable condition which developed suddenly in a 57-year-old woman, in whom the only other abnormality was a basal metabolic rate of +20%. Apparently there were no thyrotoxic manifestations, and there are none in our case.

Hypertrichosis lanuginosa and the present case have in common the lanuginous hair. Apart from this the cases differ, for in the former disease the abnormality is congenital, all the hair is lanuginous and the disease is inherited as a dominant characteristic. In the present case the hypertrichosis has been acquired in adult life, the terminal hair is normally developed, and there is no suggestion of inheritance.

FIG. 1.—Lanugo hair on the face, shoulder and trunk.

FIG. 2.—Lanugo hair on the nose, lips and chin.

We are indebted to Mr. K. Titterington for the photographs.

In considering the ætiology of our case the occurrence of a carcinoma of the bladder preceding the hypertrichosis cannot be ignored, particularly since we know that the growth has not been completely eradicated. The histology of the tumour shows a carcinoma of the bladder, and there is no question of a spread to the bladder of an adrenal or ovarian growth. The nature of the hypertrichosis, the normal menstruation and normal ketosteroid excretion support this view. It is possible that she has a latent metastasis in some site unknown which has produced this unusual and unfortunate result.

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Dr. R. N. R. Grant: I would like to draw attention to a case shown by H. S. Le Marquand and G. L. Bohn to the Section of Endocrinology (1951, *Proc. R. Soc. Med.*, **44**, 155): a man aged 61 who had developed a similar growth all over his body. He had had a large ulcer in the duodenum for which a partial gastrectomy had been carried out. Five months later he had developed another ulcer and a further partial gastrectomy was carried out. It was between this operation and the completion of his gastrectomy for a third large ulcer that he developed this condition. Formerly he had had a marked male alopecia which, in addition to this growth, had regrown. The question was raised as to whether there was a link between pathological conditions of the gastro-intestinal tract and the skin in this case, in the same way as there appeared to be in cases of acanthosis nigricans.

POSTSCRIPT (June 1951).—Since this case was shown she has been under the care of Professor J. S. Mitchell for radiotherapy on account of bleeding *per rectum* due to involvement of the intestine by secondaries.—A. L.

Subacute Systemic Lupus Erythematosus.—STEPHEN GOLD, M.B.

Mr. S. H., aged 38, in January 1950 noticed a rash over his body consisting of pink, non-irritating patches, which he attributed to eating shell-fish. He had always been subject

to attacks of coldness and numbness of his hands to which he paid scant attention. In March a red scaly rash developed on his face so he attended the West London Hospital where it was diagnosed as lupus erythematosus of superficial type, and after a period of observation he was started on intravenous gold injections (Myocrisin, 0·01 gramme) at weekly intervals. After the second injection the rash spread, he became ill and febrile and complained of pain and stiffness in different joints so he was admitted to the West London Hospital and discharged after one month when he had improved. On discharge there had been a subsidence of fever, the acute spread of the rash had cleared and the joint symptoms had improved.

During the next few months he became conscious of painful, tender glands in the groins, axillæ and around the neck; he was losing weight, feeling weak and ill and complaining bitterly of pain, stiffness and swelling of joints, particularly the wrists, fingers, elbows, knees and the neck. He also noticed a recurrence of the original rash on his trunk and limbs, blisters had started to develop on top of some of these urticarial papules but this bullous element was for the most part confined to the upper chest, shoulders and back.

He was admitted to St. George's Hospital on September 27, 1950, when he was found to present: Small atrophic area on left cheek; pronounced malar flush but no scaling or atrophy; heavy scaling over upper pinnæ but no follicular plugging; tender, enlarged inguinal, axillary and cervical glands; active arthritis with swelling of two separate joints of left hand; scattered urticarial papules over the body. These did not itch. Tense bullæ had developed on the summit of some (Fig. 1).

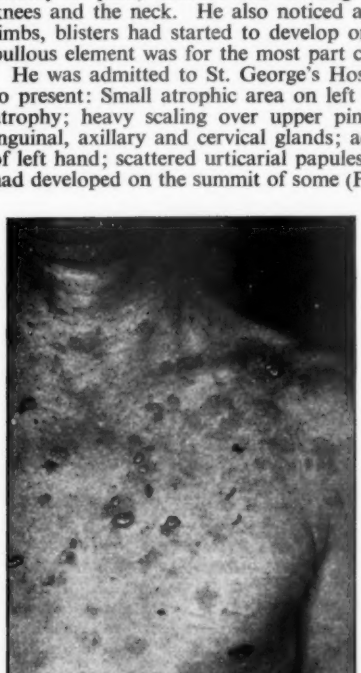

FIG. 1.—Photograph January 1951, showing urticarial and bullous lesions.

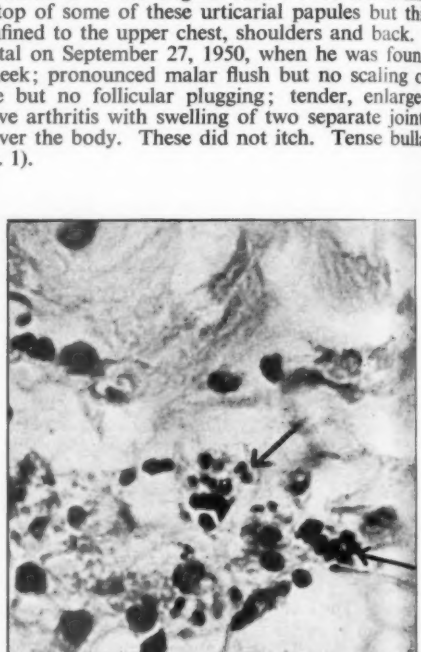

FIG. 2.—H. and E. × 850. Cellular infiltrate at base of skin bulla. Arrows indicate nuclear fragments staining positively with Feulgen stain.

Investigations revealed: Low grade, irregular fever (up to 100° F.).

Urine showed traces of albumin irregularly. Centrifuged deposit showed R.B.C. but no casts or W.B.C.

Blood: R.B.C. 5,100,000; Hb 85%; W.B.C. 4,000. Polys. 52%, lymphos. 30%, monos. 14%, eosinos. 4%. E.S.R. 48 mm./one hour. No cold agglutinins. Direct Coombs test negative.

Serum proteins: Albumin 2·4 grammes. Globulin 4·1 grammes. A/G ratio 0·6/1·0.

Urinary excretion of 17-ketosteroids 8 mg./twenty-four hours.

Gland biopsy revealed post-inflammatory fibrosis.

Two biopsies of skin were taken. The first of an urticarial papule showed nothing distinctive. The second involving a bullous lesion showed nuclear fragments (hæmatoxylin bodies of Gross) around the dermal vessels. Some of these have been ingested by leucocytes and are tissue lupus erythematosus (L.E.) cells (Fig. 2).

The following investigations showed normal results: Chest X-ray. Tuberculin reaction. Electrocardiograms (repeated). Serum potassium, sodium, calcium, phosphorus and

chloride. Blood non-protein nitrogen. Liver function tests (other than serum proteins). Urea clearance test (van Slyke). Uric acid, creatinine, and creatine excretion. Blood Wassermann and Kahn.

While in hospital he continued to suffer from a "flitting" arthritis and the joint symptoms were his major complaint. The urticarial rash as well as the bullous element fluctuated. Frequently there developed painful nodules in the palms, finger tips and thenar and hypothenar eminences. They were evanescent and not unlike Osler's nodes.

At no time has there been any clinical suggestion of involvement of heart, lungs, pericardium or pleura.

Medication.

(1) *Antihistamines*: Two periods of a week he received Phenergan 200 mg. daily. There was no effect on any symptom.

(2) *Lugol's iodine* was given as advocated by Cannon for three weeks with no effect.

(3) *Salicylates* were given as calcium aspirin, grains 80 daily. This controlled the joint pains appreciably but had no effect on abnormal biochemical and blood findings.

(4) *Testosterone propionate*, 25 mg. daily were injected for ten days. There was no effect.

(5) *Dehydro-iso-androsterone*, in doses of 50 mg. daily for one week had no effect.

(6) *Penicillin*, 600,000 units, daily for six days had no effect.

Throughout these periods dermographism remained marked, but the histamine wheal was normal. On three occasions heparin was injected intravenously (10,000 units) and by repeated estimations of prothrombin time it appeared that heparin was neutralized rapidly. Skin spreading time as determined by intradermal injection of hyaluronidase using Evans Blue and human hæmoglobin as indicator showed marked hyaluronidase inhibition (probably non-specific).

L.E. cells (Hargrave's) have not been seen in peripheral blood on three occasions nor has the Moffat-Barnes test been positive.

One new clinical feature had developed which was to recur irregularly. This was attacks of conjunctivitis ushered in by pain over and in the eye. The swelling became marked and the injection heliotrope in colour. Never have any retinal lesions been seen.

Cortisone therapy was started on January 1, 1950, in doses of 100 mg. daily. The response was noticed within forty-eight hours, joint pains vanished, rash disappeared and a feeling of well-being to a degree of euphoria was evident. When the dose was lowered to 50 mg. daily symptoms recurred so the dosage was increased again and on this higher dosage he remains relatively free of symptoms.

The response as detected by laboratory tests showed all the changes that are expected to occur: Rise of white cell count, depression of erythrocyte sedimentation rate, fall of serum globulin (later to rise), retention of sodium and chloride with fall of serum potassium. Urinary excretion of uric acid and 17-ketosteroids increased.

Comment.—This patient showed several unusual features. Urticarial papules which tended to develop into tense bullæ formed the major part of the eruption. These lesions did not itch but were associated with evanescent and painful swellings of the palms and soles. There has been a constant eosinophilia in association with a leucopenia. There is no suggestion of light sensitivity and the rash, joint pains, attacks of conjunctivitis and a dragging discomfort in the enlarged axillary and inguinal glands are his main complaints. It is interesting to note that Klemperer and his associates (1935, 1941) regarded urticaria and eosinophilia as extremely uncommon features of this disease, though it seems that they have modified their views more recently. Semon and Wolff (1933) were the first to report ocular involvement in lupus erythematosus in this country and conjunctivitis is now recognized as a not infrequent accompaniment; each attack in this patient was heralded by severe intra-orbital and supra-orbital pain.

He has been extensively investigated and subjected to a variety of therapeutic modalities with little success until the administration of cortisone was started in early January. The immediate response to 100 mg. daily was diminution of joint pains, feeling of well-being, increased weight and the usual biochemical and hæmatological findings associated with active physiological response to gluco-corticoids. The albumin/globulin ratio returned to normal on one occasion. With reduction of dosage symptoms returned.

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Dr. H. Haber: The section shows a subepidermal bulla, the base of which is formed by a very œdematous papillary body. The interesting feature of this section is the presence of nuclear debris. This is to be found both extra-cellular and intra-cellular. The Feulgen test performed by Dr.

Gold confirms nuclear chemistry of the debris. We are dealing here most probably with a L.E. phenomenon within the tissue.

Dr. F. F. Hellier: Might I utter a warning? cortisone is being used in a variety of cases. I had a patient with typical acute lupus erythematosus who was put on cortisone; within four days the temperature was down, she was feeling very much better and wanted to get out of bed; she did so and within a day or two she developed auricular fibrillation. These people have been long in bed with high temperatures, their hearts must be damaged, but they get an intense feeling of well-being and they want to get up. Similar examples have been described by Hench; when rheumatoid arthritic patients have cortisone, they feel marvellously better but they may not have walked for years so that when they start striding out they may get fractured bones. In other words, lupus erythematosus patients, although they feel well, must be treated as if they were still poorly and their heart muscle carefully nursed.

Dr. Daphne Anderson: I have thought that this might be a case of periarteritis nodosa. It is a disease occurring more commonly in a male; he has an urticarial eruption and he has an eosinophilia.

Dr. R. M. B. MacKenna: The use of cortisone is perhaps more difficult than one can appreciate by reading the literature. Recently I obtained some cortisone for the treatment of a woman suffering severely from pemphigus vulgaris. Before using the drug I obtained certain valuable information from Dr. P. O'Leary of the Mayo Clinic which indicated that not only was this disease likely to relapse after the cortisone was withdrawn but also that exacerbations might occur during treatment.

We gave our patient 100 mg. and within twenty-four hours the drug appeared to act as a provocative agent, for she developed a large number of bullæ. Never before had she developed so many fresh lesions within so short a period. The dose was repeated with the same result. 50 mg. also appeared to cause an exacerbation. Cortisone was then stopped, but several weeks later was again administered in doses of 100 mg. a day; on this occasion great amelioration occurred, but relapse eventually ensued, despite the continuation of cortisone treatment.

In reporting this case I have been careful to state that the cortisone "appeared to act as a provocative agent", for to say that it did so act as a provoking factor would be to argue fallaciously on the *post hoc ergo propter hoc* basis. Nevertheless this case suggests that the matter of how individuals react to cortisone in various phases of the disease may have to be considered.

Dr. Gold, in reply, said: The diagnosis of periarteritis nodosa was considered. This man's illness started as discoid lupus erythematosus which became systematized under the influence of gold injections. Lymphadenopathy, leucopenia and absence of hæmaturia, hypertension or peripheral neuritis supported such a diagnosis. In reply to Dr. Hellier I can say that this patient is suffering from the subacute variety of the disease. He has never been confined strictly to bed, his temperature has not been more than 100° F. and there has been no clinical evidence of myocardial or endocardial disease. Serial E.C.G.s have supported this.

We were mystified by the relapse occurring while still on cortisone, even when the dose had been put up to the original one of 100 mg. a day. The same batch kept under the same conditions was used throughout. Subacute cases are notorious in their less dramatic response to ACTH or cortisone it seems.

POSTSCRIPT.—In spite of a gradual tapering off from cortisone there was a marked "rebound flare", during which time "L.E. cells" were demonstrated in the patient's peripheral blood and the Moffat-Barnes test was positive. The patient has now remitted and he is back at work.

A Paper on **Xanthelasma Palpebrarum: a Tumour of Sebaceous Glands** was read by Mr. Eugene Wolff.

(This will be published in the *British Journal of Dermatology*.)

The following cases were also shown:

Tricho-epithelioma and Syringoma.—Dr. E. A. FAIRBURN (for Dr. F. R. BETTLEY).
Tuberculoid Lepra.—Dr. E. COLIN-JONES.
Animal Ringworm, Showing Kerion in Hairy Region and Erythemato-squamous Reaction on Open Skin.—Dr. C. H. WHITTLE.
Lupus Erythematosus Profundus.—Dr. DAVID I. WILLIAMS.
Behcet's Disease.—Dr. L. FORMAN.
Lupus Vulgaris of the Leg with Elephantiasis.—Dr. D. C. TURK (for Dr. L. FORMAN).
Lipomelanic Reticulosis.—Dr. PETER BORRIE and Dr. HENRY HABER.
Pseudoxanthoma Elasticum.—Dr. P. D. SAMMAN.

(These cases may be published later in the *British Journal of Dermatology*.)

United Services Section

President—Sir GORDON GORDON-TAYLOR, K.B.E., C.B., F.R.C.S.

[*February* 9, 1951]

DISCUSSION: THE TREATMENT OF BURNS IN LARGE NUMBERS

The President, in opening the meeting, said that the subject of the present discussion was "The Treatment of Burns in Large Numbers". According to the familiar Greek legend Prometheus stole fire from heaven and brought it to earth, incurring thereby the wrath of Jupiter. Fire had proved both a boon and bane to mankind. There had been occasions in human history when burns occurred *en masse*. He need only refer to the Biblical instance of Sodom and Gomorrah and to the results of fires produced by enemy action in the 1939-45 Armageddon. Various instances of burns in large numbers would be known to many of those present.

To-day the crust of civilization was very thin, and underneath were burning the primæval fires of hatred. Some of those present might recall a surgical mission to Russia in 1943; the mission was informed by the Russians in all sincerity that the question of the treatment of burns had not proved a great problem with them, and there was nothing that could be said to shake them in that statement.

It was not without some interest to remember that when Prometheus was chained for bringing down fire to earth, the bondage took place in the Caucasus, and vultures continually tore at his vitals. It might be that in days to come the eagles of the R.A.F. and the American Army might act in like fashion against bellicose hotheads who wanted to bring down fire upon mankind.

Lieut.-Colonel Edwin J. Pulaski.

The purpose of this presentation is to report our experiences with the exposure (open) method in the treatment of burns, with particular emphasis on (1) types of cases suitable for exposure treatment, (2) problems of application of the method, and (3) its advantages and disadvantages.

PRINCIPLES OF TREATMENT

As in all techniques of burns management, prevention and treatment of shock takes precedence over local therapy. Susceptibility to shock bears relationship to extent of injury. We have found it practical to modify the Berkow scale for the purpose of making a quick estimate of total burn surface. The body is divided into sectors, all of which, except the perineum, are worth 9%, or multiples thereof, as follows: head and neck, 9%; each upper extremity, 9%; each lower extremity, 18%; anterior and posterior trunk, 18% each; perineum, 1%. The extent of body burn determines blood and electrolyte fluid requirements, which are given according to formulations designed to maintain a urinary output of 40 to 60 c.c. per hour. Cannulation of a vein for fluid replacement is desirable. In order to obtain

accurate measurements of the urinary output, we prefer to insert a catheter into the bladder of any patient with a burn of more than 25% of the body surface.

Next to stabilization of the patient, prevention of infection and maceration is of the utmost importance. It is vital to intelligent burn therapy to recall that burn injury is the largest of open wounds, for which reason the threat of infection is ever present until a healed wound has been accomplished. The pathways of infection in burns include the burned tissues and surrounding intact skin as well as the unprotected hands and respiratory tracts of patient and attendants. Infection is the most important factor in conversion of partial to full thickness burns. The purpose of cover over a burn surface is to block exogenous pathways of infection. The purpose of exposure, paradoxical as it may seem, is prevention of contamination from becoming wound suppuration. It is based on the well-known principle that bacteria cannot tolerate the deleterious effects of drying and sunlight. Furthermore, pabulum for bacterial growth is reduced to a minimum by meticulous excision of all loose or detached epithelium and gentle cleansing of the burn surface. The natural antibacterial properties of plasma exudate, enhanced by antibiotics, assist in elimination of residual micro-organisms. In patients receiving penicillin intramuscularly we have measured up to 1·0 unit of penicillin per ml. of exuding plasma. Topley and associates have demonstrated aureomycin in excess of 1 microgram in burn exudates of patients treated with aureomycin 250 mg. six-hourly by mouth. The drug levels achieved are bacteriostatic for the great majority of hæmolytic streptococci and hæmolytic coagulase-positive micrococci which commonly predominate initial burn bacterial flora.

Conversion of plasma fibrinogen to fibrin in twenty-four to seventy-two hours results in coagulation of the exudate with formation of a tough eschar, which, in turn, protects the burns from further contamination. Rest or avoidance of movement, as well as other trauma, and elevation of extremities to minimize œdema, are factors of influence in promoting rapid, complete formation of this eschar.

The Exposure (Open) Treatment of Burns

Eighteen months ago, while visiting in the British Isles, our attention was called to the exposure or open principle of burn management which had been reintroduced a few months earlier by Wallace of Edinburgh. It had been used in the United States at least fifty years ago and had been discarded after the introduction of paraffin wax and Ambrine treatment of burns in 1914.

This report is based on a clinical trial of the exposure method in 131 patients. 65 were hospitalized in Brooke Army Hospital and were seen mostly within one to twenty-four hours after injury. The other 66 were injured in Korea and were seen at Tokyo Army Hospital on an average of four and a half to seven days post-burn. The regimen of management was the same in both groups. Clothing or dressings are removed, preferably using aseptic precautions, as soon as the patient is seen, and gross dirt is washed off the injured area with large quantities of warm water and some detergent. We prefer the use of hexachlorophene (G-11) in a base of vanishing cream, but it seems that the use of a bland white soap is also satisfactory. All blisters are opened and all detached epithelium is removed. Both cleansing and debridement are carried out as gently as is consistent with thoroughness, to avoid trauma to surviving epithelium by over-zealous scrubbing. In cases not grossly soiled, cleansing and debridement may not be necessary. If the patient has been burned recently, morphine by the intravenous route provides sufficient analgesia. If the burn is older, light general anæsthesia is usually necessary. Tetanus antitoxin 3,000 units, and procaine penicillin G, aqueous, 600,000 units intramuscularly, are given on admission. Penicillin in the same dosage is continued for an additional four days and thereafter only on specific indication. After debridement, the patient is placed in a bed in the position which best exposes the affected side. Sterile sheets are not necessary.

It is reiterated, if the patient is in shock on arrival, he is placed between clean sheets and treated intensively for shock. Debridement is postponed until the general condition has improved.

The success of the method depends largely on how effectively complete exposure, relative immobilization and elevation can be achieved.

(1) *Extremities.*—Elevation of extremities prevents additional œdema formation by aiding venous return. Burns of the configuration which provide an uninjured area on which to rest present no special problem. If the feet and ankles are not involved, the leg and thigh can be elevated by resting the ankles on several pillows. In this manner, circumferential burns of the lower extremity up to mid-thigh can be treated satisfactorily by exposure. In burns involving the hand we now feel that most patients can be encouraged to lie in bed with the elbows flexed and hands elevated. It is of paramount importance that

wrists be kept in a position of function and metacarpophalangeal joints in flexion. It is highly desirable to have the crusts form with the hand in this position. After the crust has formed, hands are fairly well held in this position. For circumferential burns involving the upper arm and upper thigh, exposure in our hands has not been altogether satisfactory, particularly when other regions of the body also are burned.

(2) *The trunk.*—Burns involving only one side of the trunk are managed satisfactorily by the exposure method, while circumferential burns pose a real problem. We have handled some of these by placing the patient on one side until complete crust formation has taken place. The patient is then turned and allowed to form a crust on the other side. This regimen leaves much to be desired, and particularly so if the upper extremities are burned as well, because the crust frequently cracks and thereby invites infection. Problems inherent in closed methods of treatment of the buttocks area are largely eliminated by exposure and our results have been good.

(3) *The head.*—In general, results with treating burns of the face have been most gratifying. If the eyelids are involved, contracture is a serious threat. Irritation of the cornea due to inability to effect complete closure of the lids, corneal ulcers, and finally ectropion may occur. Tarsorrhaphy performed early will frequently prevent these complications and, in the deep burn, will provide optimal conditions for early grafting and correction of the deformity. With burns of the neck hyperextension and relative immobilization are important for uncomplicated crust formation.

In the uncomplicated case, a crust forms in twenty-four to seventy-two hours. A warm environment will tend to delay the formation of a crust, while cold appears to hasten it. A good crust is dry and completely painless. Spontaneous desquamation of the crust over partial thickness burns generally takes place between the eighth to the sixteenth day. The average healing time for partial thickness burns is fourteen days after exposure.

In mixed partial and full thickness burns, the crust tends to remain firmly adherent in the full thickness areas. We have usually delayed excision of crusts until the twenty-first day after burning and never later than the twenty-fifth day.

Discussion.

Partial thickness burns up to 30% of body surface and involving predominantly one side of the body are particularly suited for treatment by exposure, as are burns of the head and buttocks. If the regimen as outlined above is adhered to, these types of burns heal with a minimum of discomfort to the patient and minimal nursing assistance. Loss of weight and debilitation are less frequently observed. Particularly striking is the observation that suppuration is uncommon and that the characteristic odour associated with infection in burns becomes hardly detectable. In consequence, conversion by infection to full thickness skin loss rarely occurs. The opportunity afforded by daily critical inspection of the burn crust forewarns against threat of infection in cracks, with the result that suppuration, if it occurs, can be prevented from becoming diffuse.

On the basis of our experience, particularly in Tokyo Army Hospital, we now regard one week after injury as the upper limit of applicability of the exposure method. It cannot be overemphasized that a granulating wound is unsuitable for treatment by exposure.

Several aspects of exposure treatment warrant comment. Care and ingenuity are required to obtain free exposure to air of burns of complicated distribution. Co-operation of the patient is essential. An unco-operative patient, adult or child, will frequently defeat the principle of treatment by undue movement, soaking of the crust by incontinence and the like. Patients are particularly susceptible to draught and often complain of chilliness the first day or two after exposure. Curiosity is another problem, and it affects physicians and nurses as well as patients and their visitors. It is a considerable temptation to become impatient with the natural rate of separation and to lift off the eschar. When this is done, newly laid down epithelium is pulled off with it, bleeding ensues and contamination, which is often followed by infection, is the result. The temptation is less if, as separation occurs, curled up, free crusts are trimmed.

In our hands circumferential burns of the trunk have shown evidence of infection because either the crust became cracked or formed incompletely. To date we have no solution to this problem. In a few instances contraction of the crust over full thickness burns of the extremities has given rise to ischæmic pain. Full thickness crusts over the chest may at times cause mechanical embarrassment of respiration and require incision.

Finally, results obtained with the exposure method, as with any other method, bear a direct relationship to the thoroughness with which details of treatment are carried out.

CONCLUSIONS

While the experience with the exposure treatment of burns at Brooke Army Hospital and Tokyo Army Hospital has been generally satisfactory, it is not possible to say at this time that this is the best technique for all types of burns under all conditions. This method, however, does appear to be highly satisfactory for burns confined to one side of the body and for burns involving the head, neck or perineum.

[**The Exposure (Open) Treatment of Burns.**—EDWIN J. PULASKI, Lieut.-Colonel, CURTIS P. ARTZ, Major, and JOSEPH R. SHAEFFER, Colonel, Medical Corps, U.S. Army,[1] and WILLIAM E. HUCKABEE, Lieut. (j.g.), RICHARD C. MITCHELL, Lieut. (j.g.), Medical Corps, U.S. Naval Reserve, and JOSEPH P. RUSSELL, Colonel, Medical Corps, U.S. Army,[2] This full paper has appeared in the *U.S. Armed Forces Medical Journal* (1951) **2**, No. 5, p. 769.]

[1]From the Surgical Research Unit and Surgical Service, Brooke Army Hospital, Fort Sam Houston, Texas.

[2]From the Surgical Research Unit and Surgical Service, Tokyo Army Hospital.

Surgeon Commander D. F. Walsh, R.N. read a paper for **Surgeon Commander W. V. Beach, R.N.:** Blast injuries and flash burns due to high explosives (H.E.) have, of course, long been a serious factor in war at sea; but in field warfare the modern tendency has been to replace the H.E. bomb by the phosphorus and petroleum types, thereby increasing the proportion of casualties due to thermal effects. Although it is impossible to differentiate accurately between the relative morbidity of the flash component, as opposed to the contact burn, of these newer types of explosives, it is reported from Korea that, following the use of petroleum and phosphorus bombs, only 25% of deaths were due to blast while 59% were due to burns. Following an atomic explosion, outside the lethal 1,000 yards radius, blast and flash will not be synchronous, since blast quickly settles down to travel with the speed of sound; so, there is every reason to hope that by educating the public the majority of flash burns may not be complicated by blast injuries.

The second factor which may be associated with flash burns in wartime, is the concomitant ionization radiation from the atomic bomb explosion. It was found at Hiroshima and has since been verified experimentally, that the clinical course and prognosis of all burns are adversely affected by exposure even to low doses of radiation. As it is an ever-present danger of the plutonium bomb, and the imminent menace of the hydrogen bomb against which we must prepare ourselves, I shall devote most time to the flash burn as caused by nuclear fission.

During the past few years, as a result of greater familiarity with the subject, the estimate of casualties following an atomic air burst over a large city, has been greatly reduced. Casualties are now expected to number from 10,000 to 50,000 and not 250,000 as formerly forecast. Several factors would influence the size of the casualty list, such as (1) warning of the explosion; (2) the provision of adequate shelters; (3) the time of the day at which the explosion occurred; (4) the focal site of the explosion. It must be remembered that these figures are *only estimates* and that they do not allow for either bombs of a more powerful type than that used at Hiroshima, or for multiple simultaneous atomic explosions.

A large percentage of these surviving casualties will suffer from flash burns. Practically all cases of flash burns will suffer from radiation effects as well, for following an atomic explosion, the heat radiation is emitted almost instantaneously; so too the bulk of the γ radiation; but γ radiation continues to be emitted for 60–90 seconds after the explosion. Neutron radiation I am ignoring, as its range is only some 700 yards and survival at that range can only be expected for those in deep shelters.

From the foregoing it will be seen:

(1) That while the majority of flash burns will be complicated by radiation, with training of the population to seek shelter even *after* the explosion, exposure to the full intensity of the radiation hazard can be greatly reduced.

(2) Amongst the surviving victims, it can be broadly laid down that, the more severe the flash burn, the greater will have been the dose of radiation received, with resultant poorer prognosis, and requiring appropriate modification of systemic treatment along accepted lines.

A warning here, however, as the effects of radiation are very variable, and certain biological phenomena observed after ionizing radiation are inconsistent with known physics. Thus, the exposure which is known to cause generalized epilation is greatly in excess of the diffused radiation known to cause death; and yet, many Japanese showing marked epilation recovered.

While clothing does not afford protection against γ radiation, it is an important factor in the protection against flash. In short, the heavier the material, the greater the protection. Among the newer and more popular materials, nylon has been found effective, but rayon is a danger, due to the readiness with which it is ignited. Research is under way in America with a view to the development of light anti-flash combat clothing.

In the Royal Navy the menace of flash from H.E. has been recognized and very successfully countered by the provision of antiflash helmets, gauntlet gloves and eye visors. It is only worn during an alert and in my opinion anti-flash gear can only play a limited part in the protection of exposed, defensive personnel, when warning has been received. For this purpose I consider that anti-flash gear should be supplied to all the Forces.

With regard to civilians, who undoubtedly would provide the bulk of the casualties, much could be done by educating the public *now* to the realization of the wartime dangers of bare arms, hands, legs and faces.

A point I have not seen mentioned in regard to flash burns, is that probably they will be confined to one aspect of the body only, a matter of some importance when considering treatment.

In discussing treatment, time does not permit of any details, and familiarity with the two methods to be advocated is assumed. Similarly, statements must of necessity be concise, and even dogmatic, without the quotation of authorities.

If death, and complications due to ionizing radiation, or blast, be temporarily ignored, it will be readily be seen that, according to the distance from the flash, all degrees of burning can occur.

In my opinion the treatment of burns—in mass—will more than usually be governed by the numbers, and degree of the burns, to be treated. By this I mean that because of this factor of numbers, I am convinced that even against our wishes we shall be forced to accept modification of what we consider to be the optimum treatment for patients under ideal conditions.

Beginning with the first degree burn, and bearing in mind the probability, previously mentioned, that in flash burns only one aspect of the body will be affected, there can be no doubt that the exposure method of treatment, popularized by Wallace, should be the method of choice. It seems to matter little whether any topical application is made to these cases, or even to the mild second degree burn; so long as they are kept clean and dry, healing is generally satisfactory.

In mild second degree burns showing vesication, patients are equally satisfactorily treated by this method. I think that it is important not to excise the blisters, as is sometimes taught, but rather to prick them with a sterile needle and evacuate the fluid, leaving the epithelium as the best, and most natural, cover for the injured deeper layer of skin. Alternatively, the fluid may be aspirated via normal skin to prevent any possible infection.

So far there can be little disagreement about the satisfactory results of first and mild second degree burns treated by the exposure method; it is only when we come to the deep second degree burn, and the full thickness skin loss, that with reservation I part company from Mr. Wallace. Put as briefly as possible, I remain convinced that a more rapid return to full duty can be achieved—under ideal conditions—by the treatment of these cases by the closed pressure dressing. As Mr. Wallace and Dr. Harvey Allen—the great American exponent of the closed pressure dressings—both agree, their methods seek to achieve the same object, namely, a dry surface which will either regenerate new skin from surviving follicles, or else be fit for grafting at the earliest possible moment; but with the closed method I believe this is accomplished in a shorter time.

Dr. Harvey Allen recently reported upon 955 burned patients with a mortality of 1·7%. By his methods 85% of grafts were applied in between ten and twenty-one days. In the case of children he reports 45% closed in two weeks, and 85% closed in three weeks. These are remarkable figures, and show what *can* be achieved by the proper application of this plan of treatment.

Results both at the Birmingham Burns Unit, and in my own experience, support, even though they may not match, these claims for an earlier return to duty by the use of the absorptive dressing technique.

Additionally, the strain on the nursing staff is less with the occlusive or absorptive dressing than with the exposure method, and the patients, in *this* climate, are certainly more mobile. In my wards it would be quite impossible to expose the trunk of an ambulant patient during nine months of the year.

I mentioned certain "reservations" when I said that I disagreed with the exposure method. I myself have been using an exposure method, in selected cases and in special conditions, for over ten years. In the Tropics—at Freetown, West Africa in 1940, and in the Pacific in Hospital Ships—I successfully treated many cases of burns of all depths by exposure. *There*, it was undoubtedly *better* than the occlusive dressing which caused sweating and

overheating. In fighting ships also, battened down for long periods in warm or even temperate waters, a large size pressure dressing, such as is now being stock-piled in America, would undoubtedly precipitate heat stroke. Under these conditions, cases will *have* to be treated by the open method; though here again, for the purpose of evacuation, they will, of necessity, have to be dressed and bandaged. It is perhaps not out of place to mention here the inconvenience, or impossibility of stowing these space-consuming dressings, even when rendered non-inflammable, in a fighting ship.

Another, and probably the biggest reservation, enters when enormous numbers of flash burns have to be treated, such as may be envisaged during atomic war. Since, as previously mentioned, burns from flash will probably be confined to one aspect of the body, they will be particularly *easily* treated by exposure, having one sound surface of the skin upon which to lie. Furthermore unless the estimate of casualties is still further reduced, it may be beyond the capacity of industry, and of nursing facilities, to produce and apply *satisfactory* pressure dressings to all those in whom they may be indicated under peacetime conditions.

In my opinion the exposure method is *not* the best for the deep burn, since final healing is thereby delayed.

The Application of These Treatments to Flash Burns

The treatment of burns shock, under conditions likely to produce flash burns in mass, will probably necessitate the widespread use of plasma substitutes. Of these, Macro-Dextran has been found to be one of the most satisfactory, and it is interchangeable with plasma bottle for bottle. In America the degraded gelatins, in particular P20, have found greater favour, and this, too, has been used as an effective plasma substitute in the treatment of burns. If blood is available, I think we would do well to make *greater* use of *whole blood* transfusions in the early treatment of burns shock, than is customary in England. Apart from its value in lessening, or even preventing, subsequent burn-anæmia, material benefit will accrue in cases which may later be complicated by radiation blood dyscrasias. Experience in the recent war shows that the establishment of an intravenous drip should be well within the capabilities of a trained orderly or first-aid worker.

Cleaning the burn, except in the presence of obvious contamination, is better avoided altogether. When undertaken it must be carried out in the gentlest manner possible.

Antibiotic therapy in this country is at present limited to penicillin, streptomycin and chloramphenicol. In due course terramycin will doubtless be available. Each antibiotic has a limited anti-bacterial spectrum. Penicillin has the widest range, chloramphenicol the next—including some strains of pyocyaneus—and then Aureomycin and terramycin. Terramycin has the highest percentage of sensitive cocci and Gram-negative bacilli—as one would expect in view of the short time the drug has been used.

The relative value of topical penicillin is still in dispute. We, in this country, in most units, still favour its use in both the methods under consideration. In America, its value is doubted and reliance is placed on parenteral administration of the appropriate antibiotic in established infections. My own experience convinces me of the undoubted value of topical penicillin applied as a powder—pure—or as a cream, though in a considerably stronger concentration than was used at Birmingham. I use 10,000 units per gramme in a Lanette wax base. Untoward sensitivity has been negligible.

The need for exceptional nutritional care of patients suffering from deep flash burns is well known. Nevertheless I would draw attention to the recent work of Stare of Boston, in the administration of fat emulsions as a rapid and simple method of supplying adequate calories, and at the same time conferring efficiency of utilization of other elements in the diet.

Despite the fact that many flash burns will eventually be treated by the open method, training should begin *now* in the *proper application* of pressure dressings. These dressings are now being standardized and stockpiled in America, and, following the pattern and experience of the recent war, we shall undoubtedly have to accept supplies from them, as the biggest manufacturers in an area relatively undisturbed by bombing. Even among the medical profession, the knowledge of how properly to apply a pressure dressing is often woefully lacking. It will be necessary, under conditions of atomic bombing, for the majority of these dressings to be applied by the first-aid workers, so as to facilitate the early evacuation of casualties to dispersed centres, out of the danger zone, where definitive treatment—perhaps the open method—can be given.

In Summary

At the moment antiflash clothing is not a practical proposition for the general population against the sneak atomic bomb raid. It has continuing value for war at sea and for those manning defensive posts against expected attack.

Particularly in the neighbourhood of large encampments, or under conditions of surprise, large numbers of flash burns are likely to follow an atomic air burst.

All degrees of burning can be expected.

Severe flash burns can be complicated, and perhaps rendered lethal, by ionizing radiation. Milder burns, i.e. those farther away from the source of the flash, can, by timely action, minimize the dose of radiation.

Dispersion of casualties from the scene of the disaster to undamaged areas will be inevitable—consequently immediate treatment must be advocated with this in view, and its nature *must* be compatible with mobility.

Intravenous infusions of blood, plasma, dextran or gelatin, as available, must be started in severely burned patients, before evacuation commences and maintained during the journey.

Definitive treatment must be governed to a great extent by the numbers to be treated. It may be that we shall have no option but to treat them all by the exposure method. Certainly all superficial burns—and they will, in the nature of things, constitute the majority—should be so treated.

If conditions permit, however, all severe flash burns involving deep second degree and full thickness skin loss, or worse, should be treated by the occlusive or absorptive pressure dressings, so as to make possible that ideal in the treatment of burns—the attainment of skin cover at the earliest possible moment. This should be achieved, if necessary by early excision of sloughs, and skin grafting, in full agreement with the truth of that arresting aphorism of Dr. Harvey Allen, "The impetus to heal is quickly lost".

Mr. William Gissane said that in Birmingham they used the open method for all burns of the face and most burns of the buttock. The decision as to choice of treatment could safely be left to the discretion of surgeons experienced in the treatment of burns.

When an atom bomb dropped, another and more difficult problem confronted us. Very many, perhaps some thousands of burns, would happen in a few minutes. Burns would be complicated by the effects of blast resulting in fractures and open wounds. In open wounds including burns, it was desirable to delay the onset of infection until definitive methods of treatment could be planned. There was much to be said for the early cover of all open wounds by a closed dressing—the plaster necessary for the immobilization of an associated fracture was but another layer on the dressing. The simplest mass method for Casualty Reception Hospitals was, he believed, the cover of burns by dressings with the addition of local and systemic antibiotics at the earliest moment. Very simple, quickly applied covers of nylon fabric gloves and socks had been described by Squire and Bull and had proved efficient in use.

In Birmingham they advocated closed dressings for all serious burns of the body and extremities, for by this method an accurate assessment of the depth of all burns could be made on or about the fourteenth day, when for full thickness skin burns permanent cover by skin graft could be commenced. The aim must be to cover all full thickness burns with skin grafts early. To this end it is necessary to plan the training of sufficient numbers of surgeons in the art of split skin grafting of large areas—an art acquired only after long practice. These same surgeons should recognize when a burned area is ready to graft at an early stage—the optimum time was considered the fourteenth to seventeenth day after injury when early granulation tissue and dead collagen fibres were easy to strip and bleeding was easy to control leaving a bed most suitable for the successful take of a graft.

When a burn was really extensive, i.e. over 30% of the body area, and the same donor site had to be used more than once, surgical skill in grafting such cases was especially important.

The treatment of shock was the first priority in any plan of treating great numbers of burn casualties.

To treat shock in this emergency it was essential to train assessors capable of estimating areas of burning and prescribing the amounts of plasma transfusion in each patient. These assessors could be trained in the Burns Units now established, in perhaps a month. In an emergency trained assessors with transfusion and dressing equipment and personnel could move into prearranged buildings accessible to ambulances and rescue parties and where shock treatment could begin as early as possible.

These Assessor Teams should be mobile and in close touch with Civil Defence headquarters for direction to their site of activity.

The subsequent treatment of a large number of burns casualties presents a considerable problem, to be solved only by a close-knit organization for dispersal of all casualties after as expert an assessment as can be arranged. Minor burns should not be sent back to overcrowd Cushion and Base Hospitals, their subsequent treatment is best handled by the General Practitioner service. All deep burns of less extent than the "shock group" could, after cover dressings, be sent immediately back to Cushion Hospitals for early surgical treatment. The "shock group" is best retained for twenty-four hours for treatment before transport back. Burns with little chance of survival might be retained within the target area.

Assessors must obviously be medical men and women; transfusion teams and dressers

could be recruited from medical students, nurses, the St. John Ambulance Brigade and similar organizations.

In each region a Burns Unit could well be set up now to meet this need for trained workers.

Mr. A. B. Wallace, Lecturer in Plastic Surgery, University of Edinburgh.—Following an atomic explosion, the medical members of the fighting services will be occupied primarily with injured combatants. Should, however, an incident occur in our own country the fighting services will be called on to help to cope with civilian casualties.

The aim of a Service doctor is to get every unfit man back to fighting duty in the shortest possible time. Minor casualties, therefore, are as important to him as major ones.

In a study of the problem one of the first essentials is to adopt a simple classification for burns and the simplest division is probably into *superficial* and *deep*. *Superficial* indicates involvement but not destruction of the skin; *deep* indicates destruction of skin at some part although not the actual depth of tissue destruction. In any classification the important point is to convey the degree of injury to the skin. In atomic warfare flash burns would be mostly superficial, secondary burns from ignited clothing or from burning buildings would be mostly deep. A minor burn complicated by radiation injury becomes a major problem.

With mass casualties the treatment of extensive burns would be limited to general nursing care and interference with the care of less severe burns must on no account be permitted. This fact is of equal importance to the Services and to civilians.

With repeated atomic explosions, especially against civilians, adequate personnel, laboratory facilities and supplies of material will not be available for treatment as we know it. Some other conception of treatment is, therefore, necessary.

In the treatment of burns the control of infection is of paramount importance. Growth and multiplication of micro-organisms are favoured by the presence of moisture, warmth and darkness, while invasiveness of bacteria from the surface of the body is encouraged by moist and warm dressings, by the presence of damaged or dead tissue, by movement of the part and by lax nursing care.

Treatment should be based (1) on control of infection by antibiotics and (2) on the conversion of the burnt area to a state unfavourable for the growth and multiplication of organisms. In addition the invasiveness of surface organisms should be reduced by the avoidance of moist applications and of any but bland antiseptics, by keeping the part cool, by immobilizing it and by strict nursing care. Where possible, œdema must be limited by elevation of the affected part.

The Exposure Method

The essential features are administration of penicillin systematically, full exposure and elevation of the affected part, immobilization as far as is practicable, and abstention from all local irritants and from any form of local heating. The early formation of a scab is of paramount importance. The scab appears to have many functions: to protect against the entrance of pathogenic organisms, to provide a framework or scaffold for young epithelium, in deep burns to present a barrier to the loss of protein, salt and red blood cells. Nothing must be done to delay the early formation of a crust or to disturb its integrity.

In superficial burns separation of the crust occurs within three weeks to leave a healed surface; in deep burns within the same interval it is necessary to excise sloughs and to apply skin grafts to areas of skin loss.

The detailed treatment can best be considered under two headings, general and local.

General treatment.—The first aim is to save life by early restoration of the circulating blood or plasma volume. The methods adopted to accomplish this will be governed by available personnel and supplies.

Most children with burns of over 12% and most adults with over 18% of the body surface require intravenous therapy. Patients with burns of less than 12% and 18% respectively can obtain their fluid requirements by mouth.

Certain indications of incipient oligæmic shock appear before changes in blood pressure, hæmoglobin or hæmatocrit. These are *pallor*, *thirst* and *restlessness*, and if any one be present, fluid must be energetically administered. Assessment must be based on the clinical picture.

Loss of protein and water lasts for forty-eight hours, but the greatest loss is during the first eight hours; the fluid contains approximately half the protein concentration of plasma, and a concentration of electrolytes approximately that of normal plasma (Cope and Moore, 1947). Red cells are destroyed in a burn sufficiently deep to coagulate the dermal capillaries In an extensive deep burn this whole-blood loss may account for as much as 40% of the total volume deficit (Evans and Biggar, 1945). Therefore, whole blood must be given to all patients with deep burns, and it should replace up to half the plasma-saline requirement in the first eight hours. Increased hæmoconcentration is not considered to be a contra-

indication to the giving of blood. Otherwise plasma or plasma-substitute and saline should be given in equal amounts.

The proportional intravenous fluid requirement would be: *Superficial burn*—plasma 2; blood 0; normal saline 2. *Deep burn*—plasma 1; blood 2; normal saline 1.

In addition to the fluid so given the metabolic requirements of each patient must be met in full by giving the required amount of non-electrolytic fluid, e.g. glucose water or tea, for the age-group.

In Edinburgh, a fluid requirement table has been evolved and has given every satisfaction in peacetime conditions. For mass casualties some more simple chart might be used such as our modification of Berkow's table—the "Rules of Nine". This allows ready estimation of involved surface area, required fluid replacement and guide to satisfactory urinary excretion. For intravenous fluid replacement for burns of 18% or over adults should be given, for each 9% involved, one bottle of plasma and one bottle of saline whereas a child (at 9 years) should be given for each 9%, one half-bottle of plasma and one half-bottle of saline. The "Rules of Nine" might prove of considerable use to the Services.

Sedation is important. In the Second World War, intramuscular injections of at least ¼ grain morphine were required to ease the pain of burns.

Oxygen therapy is of little value if personnel for its accurate control is not available or inadequate. In children, administration of oxygen at the rate of 3 litres per minute by intranasal catheters has been found to be the most satisfactory method.

The application of *external heat* should be avoided.

Progress can be assessed by the return of a more normal colour and warmth to the skin, by lessening of thirst and restlessness, but the most valuable single guide to progress and to the efficacy of treatment is satisfactory urinary output. Reference can again be made to the "Rules of Nine". In the adult the mean urinary output per hour is $6 \times 9 = 54$ ml., in the child $3 \times 9 = 27$ ml.

Antibiotic therapy is essential and penicillin should be given as soon as possible, either intramuscularly or into the intravenous fluid—0·5 mega-unit should be given in each twenty-four hours.

Local treatment.—Some excellent results in burns of the face exposed to the air convinced us of the importance of the production and maintenance of a dry surface. I am convinced of its efficacy in controlling infection in areas of skin trauma, and feel that it must play some part in the treatment of burns.

Every effort must be made to get the burnt surface dry as soon as possible and to keep it dry. No irritant substances must be applied. Two techniques are possible (1) an absorptive dressing over a bland surface application and (2) exposure. Their aims are: (*a*) to procure a condition of the burnt surface unfavourable to the growth and multiplication of bacteria by (i) the production and maintenance of a dry surface; if possible (ii) exposure of the surface to light; if possible (iii) the reduction of the temperature of the surface towards that of the environment; (*b*) to apply an antiseptic which is not toxic to tissue cells; (*c*) by immobilization to provide rest of the affected part; (*d*) to limit œdema by elevation; (*e*) to make nursing care simple.

Reference has been made to an "absorptive dressing". It consists of dry gauze and liberal wool applied over tulle gras; pressure is applied by a bandage on the overlying wool but not on the tissues. The pressure gradually lessens, the wool expands and the dressing becomes increasingly absorptive. The term "pressure dressing" is unfortunate. There should be no pressure on the tissues—if there is, accidents of an unfortunate nature will from time to time occur, even in the hands of an experienced surgeon. The benefits derived from "absorptive dressings" and "drying by exposure" can be compared or related from a table.

With absorptive dressings evaporation must be permitted and nothing should be applied which would tend to make the burnt surface sodden. Burn dressings must not be allowed to remain moist and thus to encourage maceration of underlying tissues.

The two forms of treatment, far from being distinct as the term "open" and "closed" would infer, are in fact closely related and even interchangeable. Certain factors will influence the choice to be adopted, e.g. number of casualties, supplies available, geographical and climatic conditions. It has been shown that for first-aid in the field, absorptive dressings are useful; at the base hospital the dressings are removed and the burn exposed or a further absorptive dressing applied.

Where possible cleansing is carried out with 1% cetrimide or normal saline: blisters are snipped and raised epidermis is removed. The burnt surface is gently dried with gauze. For mass casualties anæsthesia cannot even be considered.

Following cleansing and drying the burnt surfaces are dusted with a powder containing 10,000 units of calcium penicillin in 1 gramme of lactose. I have the impression that provided penicillin is given regularly the local application of penicillin might be omitted.

If it is employed, it is insufflated over the burnt surface every four hours until the surface is dry (usually for forty-eight hours).

All manner of organisms fall on the burn but no harm results. *Ps. pyocyanea* and *B. proteus* have been grown on culture plates placed beside burnt surfaces. In some respects treatment becomes an exercise in how best to expose and nurse the patient, but complicated orthopædic apparatus or methods are not required. The simpler the position for nursing the better. Nursing is modified according to the parts involved.

In burns of the face the patient is nursed on his back. The eyelids, the vestibules of the nose, the lips and the external auditory canals are lightly smeared with vaselin. Any discharge from eyes, nose or ears is gently removed. After about six hours the eyelids close from œdema but the fluid is reabsorbed during the third and fourth days; this closing of the eyes leads to relative helplessness.

In burns of the neck hyperextension is secured by placing extra pillows under the shoulders or by lowering the head.

In burns of the trunk and abdomen, where possible the patient lies on an unaffected aspect. When both aspects are involved a sectional bed is convenient; the sections underlying involved portions are removed. In superficial burns where possible the patient is allowed up as early as the fourth day.

Circumferential burns of the trunk are nursed on sterile sheets and their position is changed at regular intervals to allow satisfactory drying.

In burns of the buttocks, in children, the lower extremities are raised by skin traction from gallows splints until the buttocks are off the bed. Adults are nursed prone with the legs slightly abducted.

In burns of the lower extremities the method of fixation varies according to the distribution, e.g. skin traction, suspension, plaster shells, or simple exposure without splinting.

In burns of the upper extremities the method of fixation varies with the extent of involvement, e.g. skin traction, suspension, plaster shells or simple exposure. In circumferential burns of the hands in children, good results have been obtained after suspension by traction on silk stitches passed through the finger nails.

In burns of the genitalia the patient is nursed on the back with the legs in moderate abduction.

In *superficial burns*, the crust will begin to separate about the seventh day and complete separation be completed by the third week.

In *deep* burns, at the discretion of the surgeon, the crusts overlying areas of deep burning are excised and skin grafts are immediately applied. The optimum time for excision and grafting varies with the age and general condition of the patient, and extent of the burn but whenever possible should not be delayed beyond three and a half weeks and can, when desirable, take place at any time following admission.

After seventy-two hours without treatment, burns are no doubt infected. Nevertheless they should be treated by exposure. In recent weeks 3 patients with infected burns have been admitted to my wards with raised temperatures. Exposure of the burnt surface resulted in the temperature returning to normal within four hours.

In all three, cultures demonstrated penicillin- and streptomycin-resistant *Staph. aureus*. The application of wet dressings to such burns leads to spreading and even invasiveness of surface organisms. In late cases, the crust formed after exposure tends to become heaped up here and there from escape of serum and additional crusting. The heaped-up crust should be removed daily from such small areas, to allow the escape of serum. When the infected areas become covered with flat crusts local interference is unnecessary and even harmful and the care becomes that of an uninfected burn.

The method of drying by exposure has been described in detail, but once again its interrelationship with absorptive dressings must be stressed. In one large American unit, burns of the hand are treated for forty-eight hours in absorptive dressings; bandages are then removed together with any dressings which have not become incorporated in the burn crust. Such primary dressings are left attached and exposed upon the burnt hand. In this way the two methods can be alternated, with advantage to the burnt surface and to the patient, and this plan could be adopted in war.

The outstanding feature which has justified change to the exposure method of treatment has been the added control of infection. Cultures were taken daily from the burnt surfaces of the first 200 patients. There was no infection from the hæmolytic streptococcus, *Ps. pyocyanea* or *B. proteus*. In the past eighteen months cultures have been carried out only when there was some definite indication, e.g. elevation of temperature. Once again there has been no infection from the hæmolytic streptococcus, *Ps. pyocyanea* or *B. proteus*.

Transfusions of blood in the second week or later have never been required. Loss of appetite and wasting have been absent.

Segregation of burnt patients in special wards or rooms is not essential. The average

temperature of the ward in the Royal Edinburgh Hospital for Sick Children, where many of our patients are treated, is about 64° F. If protected from draught the children are comfortable at this temperature. Adults are more susceptible to draughts and prefer a slightly higher mean temperature, but over-heating and sweating must be avoided. The method of exposure is successful in the tropical heat of Texas.

Criticisms have been made of the increased nursing required, of chilling of patients, of elaborate orthopædic positioning and of lack of applicability in deep burns. No additional nursing is required. Chilling does not occur if draughts are avoided and an even ward temperature is maintained. Elaborate orthopædic fittings are quite unnecessary and special bed frames are not essential although they are very convenient.

In warm dry climates I feel drying by exposure to be ideal; in warm moist climates it should be tried because even absorptive dressings are not suitable; during the cold seasons of temperate climates absorptive dressings should be employed until the patients can be admitted to a warm room.

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Major H. L. Wolfe said that a great deal had been heard about burns that evening, but it was important to bear in mind the number of casualties due to burns which were likely to occur. In Hiroshima there were 70,000 people killed and 70,000 injured, and of the deaths, from 20% to 30% were due to flashburn, though some of these people might have died of gamma radiation later. It had been estimated that if people were in the open (as in Japan) 65% would have burns, perhaps associated with other injuries, and of all the burns 85% would be due to flashburn and 15% to fires.

Leader-Williams and Smith (1950, *Practitioner*, **165,** 594) had estimated that in an urban area where there was a density of 43 persons to the acre—which was about the density of the inner suburbs of London and greater cities—the number of injured not affected by radiation, but including burns, if all the people were in houses, would amount to 27,000. He (the present speaker) had analysed this number as follows: That there would probably be about 12,250 major injuries, 12,250 minor injuries, and 2,500 burns, chiefly due to fires. If, on the other hand, all the people were in reinforced surface brick shelters, the total number of casualties would be reduced from 27,000 to about 1,800. Burns due to flash would occur, firstly, on all exposed parts of the person, such as the face and hands, and, secondly, there would be the danger of clothing catching fire due to flash. Flash could cause casualties up to some 2½ miles in a clear atmosphere. The number of burns that would be caused would obviously depend on the amount of protection which people had. In a civil population where people were sheltered by houses and other buildings the number of burns due to flash should be comparatively few and most burns would be due to secondary causes such as falling buildings.

Among Service personnel one of the problems to be considered was the sort of protection to be offered to these people. One could say that in a well-organized city, with people in shelters, the number of casualties due to burns should approach nil. But obviously they could not reach these ideal figures, and therefore he would leave them with an average figure for most circumstances and would say that a figure of 2,500 was a possible one under average conditions as the number of people suffering from burns. In the Services, of course, the figure would depend very much on the circumstances in which Service personnel found themselves.

Group Captain G. H. Morley said that it must be puzzling to the profession at large to know, even now, what was the proper treatment of burns. Expert opinion was frequently conflicting on material details. He would suggest that they were all agreed on one point, namely, that the best results in serious burns were obtained in Burns Centres with teams of trained persons who were both interested and experienced in their treatment and argued the finer points of technique between themselves. If this was accepted, *large numbers of unselected cases would speedily overcrowd these centres.* This must be controlled by effective preventive measures to limit the number of casualties; by expert sorting of casualties and the admission only of serious cases of burns (in this category he would include those of large area, deep burns and important location, also simpler burns that had received small doses of irradiation, for Dr. Idris Evans had taught that this combination carried an unexpectedly high mortality), and, finally, early evacuation to rehabilitation centres. Burns Centres should not be divorced from general hospitals because the combined care of orthopædic, ophthalmic, and plastic surgeons, and full laboratory facilities must be available.

How were casualties to be limited? Light-coloured clothing, non-inflammable material (so wisely demanded by Dr. Leonard Colebrook, *see Lancet*, 1949 (ii), 181), slacks to cover the otherwise exposed legs of ladies, gloves for the hands, and, he supposed, wide-brimmed

hats to shield the face—such things could only be expected to reduce casualties if the mass of the population was made fully aware that such simple matters might afford surprisingly effectual protection and make all the difference between a slight and a serious burn. This consideration appeared to indicate a preference for light-coloured uniforms for defence workers.

The main objects of treatment must be kept very clearly in mind. The first, unquestionably, was to *save life*. Plasma transfusions were of very great value in the early stages of serious burns. They should be started before the inevitable onset of shock had become clinically manifest. Transportation should not be delayed for a routine administration of plasma unless this was considered essential to preserve life during a long or difficult evacuation. There was greater realization now than during the last World War that blood transfusions were of importance in treating the *early* stages of serious deep burns.

These substances would be required in large quantities in the early stages of treatment. In view of a report to the Section of Experimental Medicine the following week on experimental work on Dextran (*see* p. 557) he felt it was out of place to do more than mention it at the moment. Work was also being done on another plasma substitute, "Plasmosan".

The second objective was to *prevent infection* of the burn from becoming established during the stage of shock therapy. This brought them to the question of first aid and the early treatment of burns, with which could be associated the treatment of minor burns. At present the advice usually given was that burns should be covered with a sterile or clean dressing to limit contamination; no unguent or medicament was advocated lest it complicated the definitive treatment.

Despite what had been said about reducing the anticipated number of casualties from atomic attack to realistic from astronomical figures, many seemed to be thinking of the effect of only one atom bomb and not of several. Further, we must not forget saturation bombing with high explosives and disruption of plant and services. Many people would be unable, for various reasons, to get early medical or skilled aid. Diverse and possibly unorthodox remedies, fashionable and traditional, would be applied to burns to the detriment of asepsis. He would emphasize also the importance of preventing infection from burns which were initially minor in extent and in location, so that these should not be converted into serious surgical lesions requiring hospital admission and diminishing the ranks of active workers.

Some form of *self-help* for the population appeared to be vitally important. He suggested that every person ought to receive and carry—in the same way as anti-gas respirators were carried during the early stages of the last war—a small 1 oz. packet of an application for burns, with, of course, appropriate directions. This would be an urgent necessity and it should be determined and prepared in advance. *Dibromopropamidine isethionate* in 0·15% suspension, in a carbowax base, was a potent antibiotic which after a few applications to a burn formed a yielding eschar which could be removed later, in the case of third degree burns, by saline packs. It did not seriously interfere with later definitive treatment; indeed, it often formed a very satisfactory definitive treatment itself, particularly for minor burns with partial skin loss. It was not unstable. Its presence, ready to hand, should give the populace a sense of preparedness which enhanced morale and lessened any tendency to panic. It would diminish the establishment of sepsis and the probability of minor cases requiring hospital care. It was also effective in the smaller wounds and abrasions, secondary infection of which was more disabling than the original lesion. In its widespread use as a topical application, even if sensitivity developed, such sensitivity would not rule out or complicate the administration of penicillin in life-saving need. He thought there was a risk of this in the ubiquitous use of penicillin creams.

He also urged that all defence and skilled workers should have issued to them some form of *protective gauntlet* on the lines of the well-tried Bunyan-Stannard gauntlet, even a small bag of oiled silk or nylon. Some such protection should be provided for burnt or injured hands whilst carrying on with essential work, fighting, or merely awaiting one's turn to receive medical attention.

The *definitive treatment* of the established serious or complicated case of burns must depend on the limits imposed by staffing and the supply of dressings. Within these limits it was better for an individual or team to use a technique with which they were familiar than to embark upon the untried. But he felt that the time had now come for all to take every opportunity to familiarize themselves with the relatively straightforward exposure technique which Mr. Wallace had found so successful in treating the burns of children. He had blazed the path; it was for them all to follow and apply this line of therapy to as many and diverse burns as possible in order to determine its full range of application, as its apparent simplicity was so very attractive.

Simpler methods than had been used in the past were necessary if they were to treat large numbers of burn casualties. There would remain a good number which would require more

elaborate techniques—the fracture cases and burnt hands in particular. It was not possible to state one routine form of treatment which could cope with the diverse character of burn cases and the complicated injuries with which they might be combined; only experience and study could arm them with those alternative methods of treatment to be applied in particular difficulty. For example, there seemed to be no easy way to obtain a good functional result in badly burned hands. The classical "claw hand", which was so useless and which resulted so readily, must be avoided.

The basis of treatment, having saved life, was to avoid or control deformity and disability. This was only achieved by rapid healing. The *early skin grafting* of burns was essential where deep skin loss was present. Success in skin grafting was a matter of control of infection, early removal of sloughs, and a thorough knowledge of operative techniques. Unskilled skin grafting was to be deplored, as valuable donor areas could so easily be wrecked. There would undoubtedly be a place for the using of homografts, of skin banks, and the storage of skin by refrigeration.

Morale must be maintained throughout treatment, function must be preserved or restored by *organized rehabilitation*. The more highly supervised and equipped the rehabilitation arrangements, the earlier could cases be cleared to them from Burns Centres. At the Vauxhall Motor Works at Luton, under the supervision of Mr. Rainsford Mowlem and Mr. J. N. Barron, he believed the output of useful work from workshops employing men who were undergoing rehabilitation for various injuries was as high as 70 or even 80% of that of the fit men. This was particularly effective for recovery of use in hands, legs, and arms, and most particularly for the maintenance of morale. There was need also for full-scale, long-term *reconstructive surgery* to repair the unavoidable deformities and disfigurements. This should be planned apart from the burns centres and would maintain a shuttle service of patients between surgical and rehabilitation centres, and work or duty.

These were very briefly the points which he suggested were of the greatest importance. With regard to divergent methods of treatment, these yielded good results in the hands of their protagonists and enthusiasts. *The greatest factor in the treatment of large numbers of burn cases was to be prepared.* Neither the essential training nor the team-work could be produced at short notice.

Surgeon Commander J. J. Keevil, R.N. (retd.) said how much he welcomed the remarks of Group Captain Morley because they were so realistic. He also appreciated the brilliance of the methods which had been described but his appreciation was tempered by the fear that they might not be ideally applied in the event of atomic war. He welcomed the suggestion that there should be sectors of sorting teams, and referred to the failure which resulted during a personal experience from the lack of that very sorting and discrimination. He was confronted during World War II with the task of landing 112 casualties at midnight at Malta. They were all transported in a fleet of twenty ambulances to a hospital fifteen miles away across country roads. Unfortunately, this hospital was receiving at the very same time casualties from another ship, with the consequence that many of the men received nothing more than rest and food for forty-eight hours—rest and food which would have been available without any strain on the hospital resources in rock tunnels only 50 ft. away from the ship. But owing to the psychological point of view, which required hospitalization and theatre facilities, it seemed inevitable that they should all be sent to hospital at that time. In any future large-scale emergency it was obvious that some discipline would have to be exercised and very much wider application of first aid would be absolutely essential.

The late Sir James Cantlie in 1910 urged a widespread knowledge of first aid. He had in mind what would then happen on the beaches and in the villages and fields in the event of a German invasion. A similar situation might return and the speaker thought their frame of mind should be adjusted to it. Unfortunately, most of the methods they had heard discussed did not admit of great mobility. He felt that in the United Services Section their researches should be directed to every method that would admit of ease of transport and application by the relatively unskilled.

Surg. Lt. Cdr. (D) John Bunyan, R.N.V.R., said that after an atomic bomb explosion there would be little or no medical care available for some days, or even weeks. Treatment must be designed which can properly be given by nursing orderlies, first-aid men and even laymen—the relatives. Asepsis must give way to antisepsis.

The *immediate* requirements for a satisfactory method of treatment of burns are: (1) Relief of pain. (2) Control of primary infection. (3) Control of inflammation and œdema. (4) Immediate protection. (5) Capable of being used in the combined fracture-laceration-burn.

The *remote* requirements are (1) Prevention of secondary infection. (2) Complete protec-

tion of the wound. (3) Early separation of slough without putrefaction. (4) Rapid healing with early restoration of function.

The *practical* requirements for a serviceable method are: (1) The materials used should be easily obtainable and capable of prolonged storage. (2) The method should be suitable for all climatic conditions. (3) Early evacuation must be possible. (4) The method must be easily understood and simple in its application.

The Bunyan-Stannard Irrigation Envelope method fulfils these requirements in nearly every way. Sodium hypochlorite may be made readily available in adequate quantities anywhere at any time. The envelopes, made from a synthetic coated silk, are easily stored, easily applied, and give complete comfort and protection. Being transparent, the wound may be inspected without removing the dressing.

A colour film was shown to demonstrate the simplicity of the initial cleansing and the application of the envelope to burns of the extremities. A case of severe body burns undergoing treatment in the Bunyan-Stannard bed-bath was shown, in which the rapid separation of sloughs was strikingly evident.

A metal bed for the Bunyan-Stannard bath was demonstrated.

Mr. Patrick Clarkson said that he had recently visited Colonel Pulaski's Special Surgical Unit at the Brooke Army Hospital, Texas. He had also seen Professor Truman Blocker's organization for Burns at Galveston, Texas, and he had had personal experience over the last year of the exposure method for treating burns. On this basis he would like to add confirmation to the opinions expressed as to the practicability of the method, and of its special value for certain cases. It appeared to be very suitable for burns in children especially those of parts like the perineum and around the mouth where dressings easily became soiled and the burns subsequently infected. He agreed with Colonel Pulaski that exposure was always a hospital procedure. In his opinion exposure was somewhat slower than other methods; the crusts, even in superficial burns, took about three weeks to separate. During this time movements of the part tended to be more restricted than when other treatments were adopted. The flexible coagulum produced by exposure did not appear to have the same tourniquet risks as a tannic acid coagulum on a circumferential burn (subsequent experience has, however, shown him that in deep circumferential burns the exposure method does in fact have a "tourniquet" effect).

He wished particularly to draw attention to one possibility in recent trends in treatment, namely, the use of ACTH in association with exposure. ACTH did appear to be able to block some of the body's reaction to injury from burns. At least some patients with extensive burns (up to 40 to 60% of the body surface) could be up and about with normal pulse, temperature, sleep and appetite from the start of ACTH therapy. This possibility extended the scope of the exposure method in allowing simple exposure from circumferential trunk burns. But the use of ACTH was not a simple story, and adverse effects could be caused by it.

In conclusion concerning local treatment, he expressed the view that under ideal conditions primary treatment, provided the method used was clean and reversible, was not of great importance. Under conditions for mass casualties exposure might have to be used very widely at base or holding hospitals; it was of great value to know before the event that it was safe and practicable.

He wished particularly to query whether they were wise in adopting a formula based closely on the percentage of body surface burnt for the calculation of fluid, electrolyte, and colloid replacement therapy. Everybody dealing with these cases knew the wide variation which different patients showed to the stress produced by a burn. He had seen on the one hand a 10% of burn develop generalized œdema; and on the other a 70% body surface burn survive with virtually no intravenous therapy. Professor Thorn had, at the National Research Council Symposium on Burns, Washington, November 2–4, 1950, drawn our attention to the fact that the response of the body to the burn stress depended not only on the local system, i.e. the local production of enzymes and the area of capillary permeability produced by them, but also on at least two other systems (the neuro-endocrine axis of the pituitary-adrenal system, and the hepato-renal system). In ideal conditions replacement therapy should be individual and based on repeated blood estimations. Of the practicable guides to the rate and amount of fluid, electrolyte, and colloid restoration, he preferred the blood pressure, the hæmoglobin percentage and the urinary output. In mass conditions some quite arbitrary guides would have to be adopted, such as a chart in which numbers of pints of intravenous fluid were equated to different areas of the body.

He could confirm the fact that the electric-dermatome was an easy instrument to work. He hoped that a supply of these instruments would be made available in this country. Not only were they of great value in general surgery, but they had greatly reduced the

experience and skill necessary for the cutting of extensive grafts; they would be invaluable for the treatment of extensive deep burns even at Burns Centres to-day. The absence of these instruments in conditions of mass burns would be a serious handicap.

One other point concerned the separation of dead tissues in the healing phase; we were still dependent on the knife and scissors, but there was now considerable interest in enzymic debridement agents. Altemeir's vegetable collagenase appeared to have great promises.

He also drew attention to the experimental evidence concerning combined exposure to ionizing radiations and thermal radiations. At Professor Everett Evans' Burns Centre of the National Research Council at Richmond, Virginia, Brooks' work had shown that the mortality in dogs exposed to such combined radiations was very greatly increased; for a 20% body surface burn the mortality was increased from 13% to 75%. Deaths in these dogs occurred particularly from septicæmia by skin organisms, cf. death from radiation sickness uncomplicated by burns in which septicæmia is most often by gut organisms.

He mentioned the risk of beta particle burns. Beta particles were not a hazard in "above-ground" explosions except in the "fall out" area as the result of fission products being brought down from the radio-active cloud in a rain storm. There were, however, real biological hazards from beta particles in "under-water" and "ground-level" explosions. He thought that beta particle skin burns, differing as they did in certain important respects from thermal burns, could not be ignored in any discussion on A-bomb warfare. Beta particle burns which had occurred in accidents to physicists in the Atomic Energy Commission's A-bomb Centres (and which would be comparable to those which might be seen in naval personnel affected by a radio-active column of water produced by an under-water explosion) were similar to those seen as the result of accidents in X-ray diagnosis and therapy. The vesiculation of the skin was late and persistent; that is, it started about two days after exposure and continued for up to five weeks. Healing by marginal ingrowth was very slow and associated with progressive and persistent sloughing of central tissues. These raw areas were poor receptive surfaces for free grafts. The end-result in fingers was a stiff atrophic prong covered by thin unstable epithelium in which genetic changes had been produced tending to late malignant degeneration. He had seen photographs of some cases where gangrene had occurred in such fingers during the second week after the burn. He believed that such a complication might be avoided by early radical and circumferential removal of the whole (non-elastic and constrictive) skin of the digit, and its immediate replacement by planned pedicle flaps from the abdomen.

Mr. David N. Matthews said that the treatment of burns in large numbers, which was the problem before the meeting, would inevitably necessitate considerable modification of treatment as practised at present on the individual case in peacetime. He thought that under such circumstances much of the local treatment would have to be performed by civilians under the supervision of doctors. If this were true there would be a great advantage in training civilian teams now. Treatment would have to be simplified as much as possible. He had recently seen the exposure method in use at Colonel Pulaski's Hospital in Texas; it was impressive; the patients were well, and healing was, he thought, quite as rapid as with other methods. He doubted, however, if it could be applied in Britain in wintertime and under wartime conditions. Moreover it was difficult to see how it could be applied if circumstances were likely to lead to the transfer of patients from one city to another. There seemed to him to be a good case for initial covering of the burnt surface with, perhaps, substitution of the exposure treatment when the patient reached a base hospital where he was likely to stay.

In view of the very large numbers of burns which some speakers had envisaged, he thought that the medical personnel would be fully occupied with the administration of intravenous fluids and strongly urged the education of the public now in a simple safe method of dressing burnt surfaces. He added that under the serious conditions which had been postulated it might be necessary, even if not ideal, for medical mobile teams to be formed. To count upon the appearance of a chain of base hospitals equipped with large burns units seemed at this stage to be over-optimistic.

The use of ACTH was giving promising results in the American Centres which he had seen and there was a good prospect that it would prove of real value if adequate supplies were forthcoming.

Sir Claude Frankau said that, in general, it was thought that in the first stages after flash burns—that is to say, when the patient was picked up and taken back to what they were going to call cushion hospitals—a closed method of treatment would be necessary. The reason for that was that the patient would have to be moved to a base hospital at the earliest possible moment. He might perhaps have to be moved 100 miles, and he doubted

whether he would stand, even in the "heat" of an English summer, travel in a practically nude condition for that distance.

His committee thought, therefore, that the closed method of dressing would be necessary and that what was rightly called the Colebrook method of dressing—that is penicillin cream—would probably be the best method. There were other methods under consideration.

A rule-of-thumb method of resuscitation would be presented in chart form which he hoped would be found useful.

Surgeon Captain S. G. Rainsford desired to say a word on the question of irradiation and flash burn. As Mr. Clarkson had suggested, it would be a mistake to rely entirely on antibiotics and ignore any other bacteriostatic.

Recent experimental work carried out on animals in the U.S.A. showed that the mortality from burns was enormously increased if concurrently the animals received relatively small doses of radiation. This effect was apparently due to interference with the normal immunological response to infection.

A number of methods and techniques for the treatment of burns had been described, all of which had had some measure of success, and all of which mainly depended for this success upon the use of an antibiotic, in most cases penicillin. In all these cases, however, it could be assumed that the normal defensive mechanism of the body against secondary infection had not been unduly suppressed. In view of the American work it was problematical whether the results of such treatment would be anything like as good had these patients been irradiated as well as burnt. He was not sure therefore that the policy of ignoring anti-sera was wise. It was highly probable that the concurrent exhibition of anti-sera as well as antibiotic might be found necessary as a treatment of burn cases who had also suffered from some degree of irradiation.

With regard to control of body fluids he had had some experience in a cholera epidemic with rapid dehydration in which the amount of intravenous fluids required was controlled by measuring the specific gravity of the blood by means of Phillips and Van Slyke's copper sulphate method. Its value in dealing with large numbers of cholera cases was tremendous. There was a very low mortality and he could not see why this should not be adopted in other conditions when they were faced with large numbers of casualties.

Mr. David H. Patey referred to some of the problems raised in the technique of exposure treatment of burns. An evaporative or absorptive-evaporative dressing might achieve the same object while at the same time affording mechanical and other protection. With his colleagues he was at present exploring the possibilities of absorptive-evaporative pastes as dressings.

Section of Medicine

President—C. E. LAKIN, M.D., F.R.C.P., F.R.C.S.

[*February* 27, 1951]

DISCUSSION ON PULMONARY HEART DISEASE

Dr. D. Evan Bedford: PULMONARY HEART DISEASE.

I shall first define pulmonary heart disease as a condition of right ventricular hypertrophy, and eventually of right heart failure, due to pulmonary hypertension resulting from an increased resistance to the circulation through the lungs. Pulmonary hypertension may have a structural or a functional basis. It may be due (1) to gross destruction of lung tissue with corresponding reduction in area of the capillary bed; (2) to obliterative endarteritis of the pulmonary arterioles; or (3) to pulmonary vasoconstriction secondary either to anoxia or to causes unknown. Given an anatomical basis such as pulmonary endarteritis, we still have to decide whether the arterial lesion is causative or merely a secondary effect of the hypertension. Evidence suggests that the hypertension is primary in some cases, but in others, for example bilharzial or carcinomatous arteritis, the arterial lesion is clearly causative. It appears that pulmonary hypertension may be initiated by chronic lung disease or by pulmonary vascular disease, and that it also occurs in a primitive form comparable with systemic essential hypertension.

Classification.—So-called acute cor pulmonale is due to massive pulmonary embolism or to rupture of an aortic sinus aneurysm into the pulmonary artery and need not be discussed further. In chronic pulmonary heart disease two factors are concerned, anoxia due to defective aeration of the blood in the lungs, and hypertension due to vascular obstruction. Following McMichael, we may group our cases on this basis into anoxic and hypertensive forms. In the anoxic form, the initial fault is in the lungs, and cyanosis of central origin occurs early, whereas in the hypertensive form, lung function is not at first involved and cyanosis occurs late, when a falling cardiac output leads to peripheral stasis. In practice, these two basic types overlap to some extent and for clinical purposes we may recognize two main groups, first, cases with gross lung disease, and, secondly, cases in which pulmonary arterial disease or dysfunction predominates. On this basis I have classified the various ætiological forms of pulmonary heart disease as follows:

(1) Due to chronic lung disease.

(2) Due to angular curvature of the spine.

(3) Due to pulmonary arterial disease, (*a*) from conditions causing an increased pulmonary flow, e.g. atrial septal defect, ventricular septal defect, and patent ductus arteriosus; (*b*) from mitral stenosis; (*c*) endarteritis of known causation such as rheumatic, syphilitic, bilharzial, secondary to miliary carcinoma, or to repeated pulmonary embolism.

(4) Primary pulmonary hypertension of unknown ætiology.

The first clinical signs of pulmonary hypertension are due to enlargement of the outflow tract of the right ventricle, namely a systolic impulse sometimes with a thrill, followed by a diastolic click corresponding to the second sound, palpable in the second and third left interspaces. A systolic murmur is usually audible and a loud and often duplicated second sound. Occasionally there is a Graham Steell murmur of relative pulmonary incompetence. Later, the right ventricle proper enlarges and the apex beat is displaced to the left. The apex impulse of an hypertrophied right ventricle is diffuse compared with the localized thrust of the left ventricle, and it may be quite forcible, but not snapping unless there is mitral stenosis. A triple rhythm is common in the later stages when signs of tricuspid incompetence may also appear. When heart failure occurs, the rhythm almost invariably remains regular as first pointed out by Parkinson and Clark-Kennedy in 1926.

Radiological evidence of pulmonary hypertension is, first, enlargement of the pulmonary trunk and hilar branches, next the conus, and finally of the right ventricle proper which enlarges to the left imparting a blunted or square shape to the apex and left heart border (Fig. 1).

The electrocardiogram provides important evidence of right ventricular hypertrophy. In the standard leads we find large pointed gothic P waves in leads 2 and 3, and right axis deviation, which may be due mainly to a vertical heart in emphysema; the T waves are often inverted in leads 2 and 3. With gross enlargement, the chest leads show a characteristic pattern (*see* Fig. 2), or sometimes right bundle branch block.

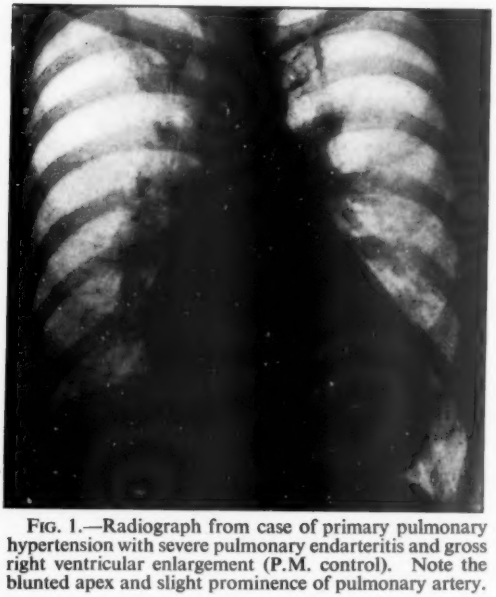

FIG. 1.—Radiograph from case of primary pulmonary hypertension with severe pulmonary endarteritis and gross right ventricular enlargement (P.M. control). Note the blunted apex and slight prominence of pulmonary artery.

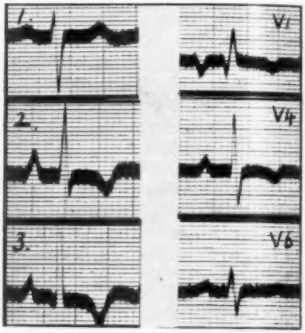

FIG. 2.—Electrocardiogram from same case as Fig. 1. Standard leads show right axis deviation and inversion of T waves in leads 2 and 3. Chest leads show pattern of gross right ventricular hypertrophy.

Finally we may confirm these clinical and other findings by cardiac catheterization. The normal right ventricular pressure is about 25 mm.Hg systolic, and mean pressure 13 mm. In primary pulmonary hypertension, the mean pressure may exceed 50 mm.Hg. This method has the advantage of demonstrating the presence of intracardiac shunts from left to right, for example in atrial septal defect which is often mistaken for pulmonary heart disease.

Clinical features.—Of lung diseases, emphysema alone or combined with bronchitis, asthma, or bronchiectasis, is by far the commonest cause of pulmonary heart disease, less common ones being anthracosis, silicosis, fibroid tuberculosis, cystic disease, sarcoidosis, primary hæmosiderosis, and, in a separate category, severe kyphosis.

In emphysema heart, the clinical course is essentially that of progressive lung disease with increasing dyspnœa, cyanosis of central type, and episodes of acute infection or increased bronchospasm. Throughout, the symptoms are pulmonary rather than cardiac, and even though congestive heart failure occurs towards the end, death is due mainly to anoxia and there is drowsiness, coma, toxæmia, and often a sudden terminal peripheral circulatory failure. In my experience, heart failure is usually precipitated by lung infection or increased bronchospasm which intensifies the anoxia. This requires emphasis as treatment should be directed to relieving anoxia and infection. In emphysema heart such as I have described, cardiac enlargement is usually slight, but in some cases of chronic lung disease the arterial factor is more important than the anoxic, and in these the right heart may become grossly enlarged. Because heart failure complicates advanced lung disease, the prognosis is bad, and Scott and Garvin (1941) found that 80% of their series of emphysema hearts died in the first attack of failure. I have, however, seen cases of heart failure in chronic lung disease last much longer than is alleged. It must also be remembered that heart failure in emphysema is more often due to hypertension or to coronary disease than to right heart failure as Parkinson and Hoyle (1937) have shown.

I should perhaps refer to the legendary condition known as Ayerza's disease. Ayerza gave two unpublished clinical lectures entitled "black cardiacs" in which he is said to have described the terminal cardiac phase of chronic lung disease. The eponymous syndrome was first officially enunciated by Arrillaga in his thesis in 1912, which he dedicated to Ayerza, and he described pulmonary arteriosclerosis secondary to lung disease. Only later was a

syphilitic ætiology suggested and confusion thereby started. The symptoms mentioned were dyspnœa, cyanosis, polycythæmia, cough, hæmoptysis, headache, somnolence, and hypercyanotic angina, associated with enlargement of the pulmonary artery and right heart, and right ventricular gallop rhythm. He stated that bronchopneumonia and toxæmia rather than heart failure often terminated the disease.

Of the primarily vascular forms of pulmonary heart disease, I have already referred to that secondary to arteriovenous shunts and to mitral stenosis. Not only are they true examples of pulmonary heart disease but they may easily be mistaken for primary pulmonary hypertension. Reversal of the shunts may cause deep cyanosis.

Of arterial lesions of known ætiology, the syphilitic variety must be extremely rare, but well-authenticated cases have been recorded in this country by Konstam (1929), and by Hare and Ross (1929). Endarteritis secondary to lymphangitis carcinomatosa, in which the primary growth is usually in the stomach and often undiagnosed, is not common and I have only seen a few cases, but the subject has been well reviewed recently by Morgan (1949). The arterial obstruction may be due to an endarteritis in vessels adjacent to infiltrated lymphatics, or to malignant vascular emboli.

Repeated pulmonary embolism is another cause of cor pulmonale which is, I believe, commoner than supposed. Brenner (1935) mentions a number of cases, Castleman and Bland (1946) recorded an important case, and I have encountered several undoubted cases. The emboli may involve the small vessels or even the larger ones.

Bilharzial pulmonary endarteritis is a common cause of pulmonary heart disease in Egypt where I have seen many cases. In patients infested with bilharzia, ova pass to the lungs as emboli and block the small vessels, causing an endarteritis of characteristic histological pattern, in which the occluded vessel is surrounded by angiomatoid formation (Shaw and Ghareeb, 1938; Bedford, Aidaros and Girgis, 1946). In the course of time, repeated embolism causes pulmonary hypertension and gross enlargement of the right heart, often combined with aneurysmal dilatation of the pulmonary artery. Cyanosis is absent.

Primary pulmonary hypertension is a rare disease but with the aid of cardiac catheterization we are able to identify it more often now than was formerly possible. It affects both sexes equally and may occur in childhood or adolescence. The last 3 cases I have encountered, all with post-mortem confirmation, have been females aged 7, 32 and 62 respectively. In one there was severe and widespread obliterative endarteritis, and in one the arterial lesion was quite trivial in relation to the size of the right heart. The usual story is of a patient with neither history nor signs of lung disease who becomes quite rapidly breathless for no apparent reason; before long cyanosis appears with cold extremities, and enlargement of the heart is found. The electrocardiogram shows the pattern of gross right ventricular hypertrophy in the chest leads, or of right bundle branch block. Within a period of six to twelve months, rarely longer, heart failure appears and cyanosis deepens. In my experience, the arterial oxygen saturation is usually somewhat reduced, e.g. 75 to 85%, but insufficiently so to account for the cyanosis which is mainly peripheral in type.

Hypercyanotic angina is an interesting symptom first described by Posselt in 1909, and mentioned by Argentine writers. One of my patients had severe attacks of constrictive pain across the chest, extending into both arms, which were relieved by putting her in the oxygen tent; another had angina of effort accompanied by severe dyspnœa, and no coronary lesion to account for it was found at necropsy. The underlying mechanism may be anoxia combined with right ventricular strain, or in some cases pulmonary embolism.

Diagnosis.—Diagnosis is easy when chronic lung disease is present, but in the primary arterial forms it is much more difficult. Having established the presence of right ventricular enlargement by radiography and by an electrocardiogram, we must have in mind and exclude other causes of pulmonary hypertension, especially mitral stenosis and congenital heart disease. An enlarged left auricle indicates a renewed search for murmurs of mitral stenosis. Atrial septal defect is a common cause of great enlargement of the right heart and pulmonary vessels and its diagnosis from pulmonary heart disease can be difficult. A pulsatile right ventricle and obvious hilar dance seen on radioscopy are suggestive and the electrocardiogram almost always shows some grade of right bundle branch block in the chest leads. In doubtful cases, cardiac catheterization is necessary to demonstrate the atrial shunt.

Idiopathic congenital dilatation of the pulmonary artery is another rare condition which may simulate pulmonary heart disease. It can only be diagnosed with certainty when catheterization shows a normal right ventricular and pulmonary arterial pressure, and excludes an intracardiac shunt. Either the pulmonary trunk or the branches may be dilated, sometimes both, and the aorta is usually small and hypoplastic. Cardiac enlargement and cyanosis are usually absent, though in some published cases cyanosis has been present. The electrocardiogram may be normal.

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Dr. William Evans: CONGENITAL PULMONARY HYPERTENSION.

Experience with cases of pulmonary emphysema has emphasized the perplexity caused by variation in the clinical course followed by individual patients. Some survive for years, whilst others deteriorate quickly and die in the face of organized treatment. This uncertainty in prognosis reminds us of our weakness in diagnosis, and of our inability to allocate cases to either group when they come for clinical examination. This is how, along with J. R. Gilmour, I came to study a series of cases of emphysema both clinically, and in a special way at necropsy where the lungs were examined histologically, and radiologically after filling the bronchial arteries, and sometimes the pulmonary arteries, with a radio-opaque substance. Patients with other causes of pulmonary hypertension were also examined, and experience with such material allows me to discuss the cases under the head of *congenital pulmonary hypertension*. It is opined here that the same mechanism is operating in most examples of gross pulmonary hypertension. Thus, it is found in primary pulmonary hypertension, and sometimes in congenital dilatation of the pulmonary artery, patent ductus arteriosus, auricular septal defect, pulmonary cystic disease, and emphysema; whether the same mechanism applies to cases of mitral stenosis with severe pulmonary hypertension has yet to be tested; I believe it will be shown that this is so, and Bayliss and his co-workers (1950) have already found that increased pulmonary arteriolar resistance plays an important part in the development of severe hypertension in mitral stenosis.

Primary pulmonary hypertension.—When pulmonary vascular disease giving rise to pulmonary hypertension has no obvious outside cause it is referred to as *primary* pulmonary hypertension. Although commoner among older subjects, it is found occasionally in younger adults. In 20 cases reported by Brill and Krygier (1941) both sexes were affected equally. The illness sets in insidiously with tiredness as the chief complaint. Breathlessness soon follows and it gradually increases. Cough and even hæmoptysis may be present.

Cyanosis is prominent and is associated with polycythæmia. The pulse is small and the blood pressure is low. Cardiac enlargement may not be obvious on clinical examination, but pulsation over the pulmonary artery is often present and is sometimes prominent. There are no murmurs unless distension of the pulmonary artery is so great as to give rise to an early diastolic murmur from pulmonary incompetence. Triple heart rhythm from addition of the third heart sound is a common finding. There is accentuation, without splitting, of the second sound in the pulmonary area. Signs of heart failure make their appearance during the course of the illness and they include full veins in the neck, crepitations over the lung bases, distension of the liver, œdema of the ankles, and even ascites. Such signs increase gradually in their severity until death ensues and this takes place suddenly. The electrocardiogram shows right heart preponderance (Fig. 1), and on cardioscopy there is enlargement of the right auricle and ventricle and of the pulmonary artery (Fig. 2).

At necropsy the clinical findings of heart failure and enlargement of the right heart and pulmonary artery are confirmed. Histologically, the smaller muscular arteries are partly, and here and there wholly, obstructed by endarteritis fibrosa. This endarteritis was found over deficiencies in the arterial walls caused by foci of aplasia and hypoplasia of the media (Gilmour and Evans, 1946). We believe that the existence of this developmental defect in the media of innumerable small pulmonary arteries throughout the lungs is the operative factor in the genesis of the endarteritis whose growth in turn is promoted by the pulmonary hypertension which it induces.

Congenital dilatation of the pulmonary artery.—This is not a common condition and many of the clinical cases reported in the literature have proved at necropsy to be instances of auricular septal defect. None the less, examples are met with from time to time and the condition assumes an innocent course unless complicated by pulmonary hypertension. The physical signs and progress of the illness are illustrated by the case of a young woman of 28 years of age admitted under the care of my colleague, Dr. Wallace Brigden. At the age of 11 years she was known to have congenital disease of the pulmonary valve. During recent

years she had noticed increasing breathlessness, and after becoming pregnant five months before, she had experienced several attacks of nocturnal dyspnœa.

There was moderate cyanosis, but no clubbing of fingers. The pulse was small and the blood pressure was 110/70. The apex beat was displaced outwards, and there was prominent pulsation in the second and third rib spaces to the left of the sternum. A systolic murmur was audible over the heart and a long and loud early diastolic murmur along the left sternal border was accompanied by a thrill. A triple rhythm from addition of the third heart sound was present in the mitral area. The electrocardiogram showed right heart preponderance (Fig. 3), and on cardioscopy there was enlargement of the right heart and great or aneurysmal enlargement of the pulmonary artery (Fig. 4).

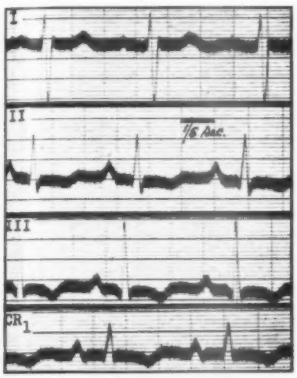

FIG. 1. — Primary pulmonary hypertension. Electrocardiogram showing deep S wave in lead I, absence of S in CR_1, and inversion of T wave in leads II, III, and CR_1.

FIG. 2.—Primary pulmonary hypertension. Teleradiogram showing enlargement of right auricle, conus of right ventricle, and of pulmonary artery, together with moderate pulmonary congestion.

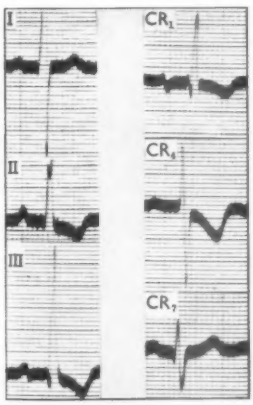

FIG. 3. — Congenital dilatation of pulmonary artery. Electrocardiogram showing deep S wave in lead I, absence of S in CR_1, and inversion of T wave in leads II, III, CR_1, and CR_4.

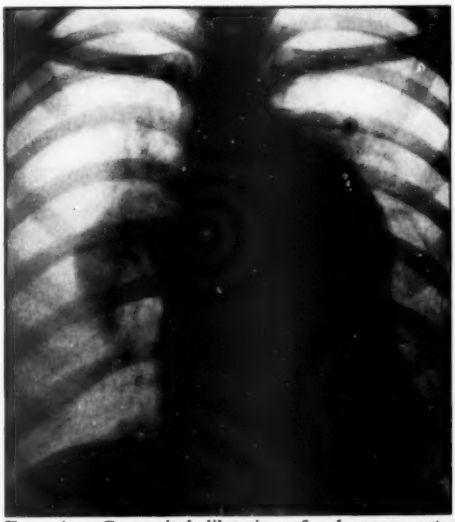

FIG. 4. — Congenital dilatation of pulmonary artery. Teleradiogram showing aneurysmal enlargementof pulmonary artery and prominence of its branches.

FIG. 5.—Congenital dilatation of pulmonary artery. Radiogram of lung after injecting pulmonary artery with radio-opaque substance.

Apart from breathlessness on exertion there were no obvious clinical signs of heart failure. She died suddenly and unexpectedly.

At necropsy the heart, weighing 18½ oz. (537 grammes), showed great hypertrophy with dilatation of the right ventricle. There was fusiform swelling of the pulmonary artery measuring 7·0 by 4·5 cm., and the dilatation also involved its branches. A radiogram of the lungs following injection of a radio-opaque substance into the pulmonary arteries showed this dilatation to good advantage as well as pruning of the terminal branches caused by obstruction within them (Fig. 5). Histological examination showed that this was the result of endarteritis fibrosa within the smaller arteries which in places showed aplasia or hypoplasia of the media.

In congenital dilatation of the pulmonary artery, therefore, the condition pursues an innocent course, unless an inherent weakness of the media of the lesser pulmonary arteries is fortuitously present, and this raises the pulmonary pressure, exciting the development of endarteritis fibrosa which in turn accentuates the state of pulmonary hypertension leading to heart failure and ultimate demise.

Patent ductus arteriosus.—Since ligature of the ductus has become routine treatment of patent ductus arteriosus, more than ordinary care needs to be taken in the diagnosis of the condition. The electrocardiogram should never be omitted for if it shows right heart preponderance some other lesion is present which by itself can produce this cardiographic abnormality; this may be an associated congenital anomaly like pulmonary stenosis, but more likely it is the result of endarteritis fibrosa of the lesser pulmonary arteries causing pulmonary hypertension.

The clinical and cardiographic signs exhibited by this syndrome are illustrated by a patient, a young woman aged 22, who had complained of breathlessness and cough for eight years; both symptoms had increased gradually, and, before her death, they had been joined by others which were the outcome of heart failure. There was cyanosis and polycythæmia, but no clubbing of fingers. Scattered rhonchi were present over the lungs, and there was distension of the liver and œdema of the ankles. The pulse was small and the blood pressure was 110/80. Pulsation could be felt in the pulmonary auscultatory area. A systolic murmur was heard along the left sternal border and an early diastolic murmur followed a second sound which did not show splitting. A triple rhythm was present from addition of the third heart sound. The electrocardiogram showed right heart preponderance (Fig. 6). Cardioscopy showed enlargement of the right heart and distension of the pulmonary artery and its branches which exhibited obvious pulsation (Fig. 7). Dyspnœa and cyanosis increased and at the end she died suddenly. In this, as in other examples in the literature (Chapman and Robbins, 1944; Douglas and others, 1947), a wrong diagnosis of auricular septal defect was made;

the characteristic machinery murmur of patent ductus arteriosus in such cases is missing because the pulmonary arterial pressure is increased and matches the height of the systemic blood pressure so that no appreciable flow of blood takes place through the open ductus.

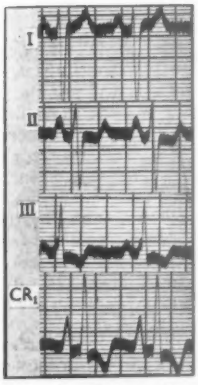

FIG. 6. — Patent ductus arteriosus with pulmonary hypertension. Electrocardiogram showing deep S wave in lead I, absence of S in CR_1, and inversion of T wave in leads III and CR_1.

FIG. 7. — Patent ductus arteriosus with pulmonary hypertension. Teleradiogram showing enlargement of right heart, pulmonary artery, and its branches.

At necropsy in this case the auricular septum was intact while the ductus was open and was 0·9 cm. in diameter. There was great hypertrophy of the right ventricle. On histological examination the lesser pulmonary arteries were found to be blocked by endarteritis fibrosa. In places this had formed over foci of aplasia or hypoplasia of the media (Fig. 8). Such congenital weakness of the arterial walls was associated in this patient with other congenital anomalies including a patent ductus, dislocation of the left kidney to the right side, unicornuate uterus, absence of the thumb in both hands, and absence of the radius in both arms.

The sequel of events in cases belonging to this group is a slight rise in pressure in the pulmonary artery from the presence of an open ductus. This produces endarteritis in the lesser pulmonary arteries over those parts affected by congenital hypoplasia, and the resulting blockage increases the pulmonary arterial tension which in turn hurries the process of endarteritis.

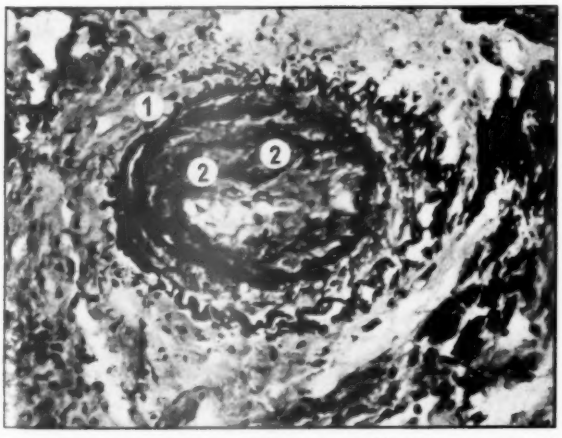

FIG. 8. — Patent ductus arteriosus with pulmonary hypertension. Section of small pulmonary artery showing aplasia of its media (1) and endarteritis fibrosa (2). × 100.

Auricular septal defect.—Auricular septal defect has often a good prognosis; it is peculiarly free from the risk of bacterial endocarditis. The onset of heart failure is sometimes caused by gross pulmonary hypertension and incompetence following obstruction within the smaller pulmonary arteries; this latter condition causes death from heart failure in earlier life. Welch and Kinney (1948) discovered only one such example among 25 cases of auricular septal defect, but Zur Linden (1924) described a case at the age of 11 months, and Wätjen (1926) one at 6 months. Longevity, therefore, in auricular septal defect depends on the degree of pulmonary incompetence and pulmonary hypertension resulting from obstruction within the lesser pulmonary circulation.

A recent case in my experience was a woman, aged 52, who was first seen fourteen years before by Sir John Parkinson on account of palpitation. A diagnosis of auricular septal defect and auricular tachycardia was made. There was no cyanosis at the time and no clubbing of fingers. During the last four years she complained that her face and lips were becoming very blue and that she was breathless. Latterly, œdema of the ankles and ascites were added symptoms. There was black cyanosis, but clubbing of the fingers was still absent. The veins in the neck were greatly distended and were pulsatile. The pulse was not small and was irregular from auricular tachycardia with A-V dissociation varying from 2 : 1 to 4 : 1. The blood pressure was 120/85. The apex beat was displaced outwards. To the left of the sternum, and especially in its lower half, a rough and loud systolic murmur was associated with a thrill, and an early diastolic murmur followed a second sound which did not show splitting. Triple rhythm from addition of the third heart sound was heard late in the illness. Clinical evidence of heart failure included breathlessness on exertion, crepitations over the lung bases, distension of the liver, ascites and œdema of the ankles. The electrocardiogram showed right heart preponderance and auricular tachycardia (Fig. 9). On cardioscopy there was great enlargement of the right heart and of pulsatile pulmonary arteries (Fig. 10). At the end death took place suddenly from heart failure following pulmonary hypertension.

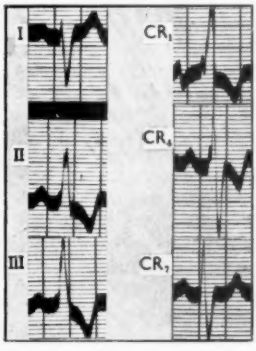

FIG. 9.—Auricular septal defect with pulmonary hypertension. Electrocardiogram showing deep S wave in lead I, absence of S in CR_1, and inversion of T wave in leads II, III, CR_1, and CR_4.

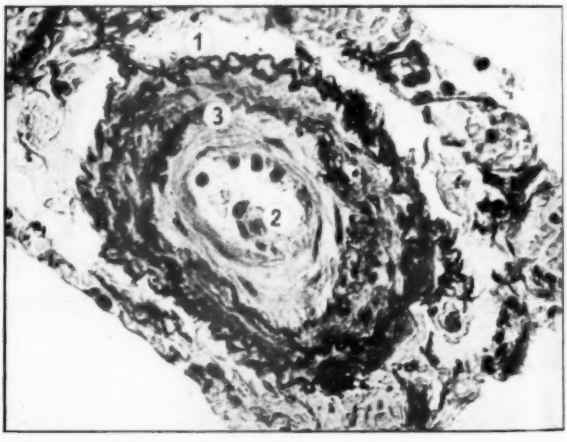

FIG. 11.—Auricular septal defect with pulmonary hypertension. Section of small pulmonary artery showing aplasia of its media (1), with recanalization (2) of endarteritis fibrosa (3) which is obstructing lumen. × 125.

At necropsy the clinical finding of great enlargement of the right heart and the pulmonary arteries was confirmed, as also was heart failure. When the pulmonary circulation was examined radiologically after injection of a radio-opaque substance, a pruning effect of the distant branches was seen. Histological examination showed obstruction of innumerable small pulmonary arteries by endarteritis fibrosa which had formed specially over segments demonstrating aplasia or hypoplasia of the media (Fig. 11). In places there was arterial thrombosis which sometimes showed recanalization, and there was intra-alveolar hæmorrhage.

Pulmonary cystic disease.—The course of this illness varies according to the extent to which the kidneys are involved and the severity of the pulmonary condition. As a rule the renal symptoms are uppermost. When the process affects the lungs in particular, it may induce pneumothorax, emphysema, or bronchopneumonia; an unusual terminal event is heart failure from pulmonary hypertension as illustrated by an Indian medical practitioner, a male aged 31. Cystic disease of the lungs had been discovered as the cause of pneumothorax

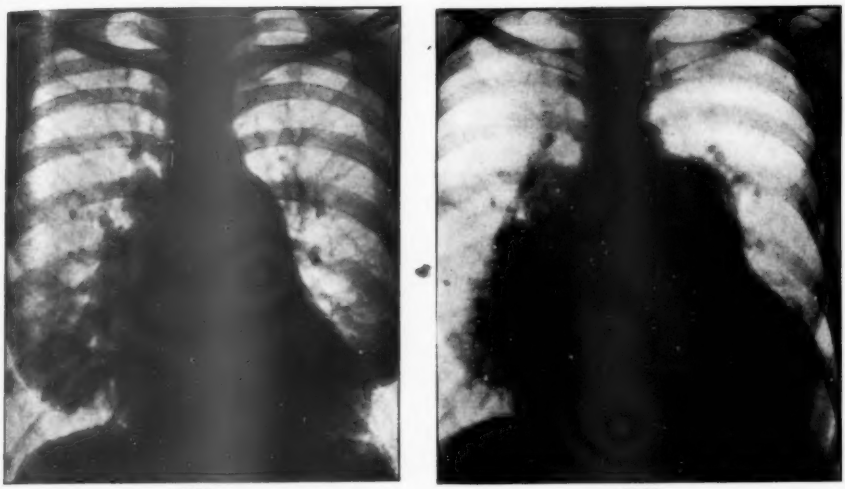

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FIG. 10.—Auricular septal defect with pulmonary hypertension. Teleradiogram showing enlargement of right heart and of pulmonary artery and its branches, and showing progressive enlargement over fourteen years.

ten years before, but three years later he recovered well enough to serve for four years in the Army. The symptoms of heart failure had only been present for two months before his admission to hospital and they had increased rapidly. He was breathless even at rest. Cyanosis could not be told, but there was much distension of the neck veins and some polycythæmia. The pulse was very small and the blood pressure was 110/85. The apex beat was displaced slightly to the left. Fine crepitations were widely scattered over the lungs even as high as the apices. The liver was distended and there was ascites, and much œdema of the ankles. The electrocardiogram showed right heart preponderance (Fig. 12) and on cardioscopy there was moderate enlargement of the right heart and pulmonary artery with pulmonary con-

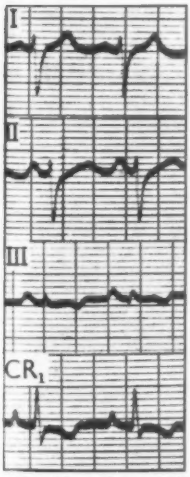


FIG. 12.—Congenital pulmonary cystic disease. Electrocardiogram showing deep S wave in lead I, small S in CR_1, and inversion of T wave in leads III and CR_1.

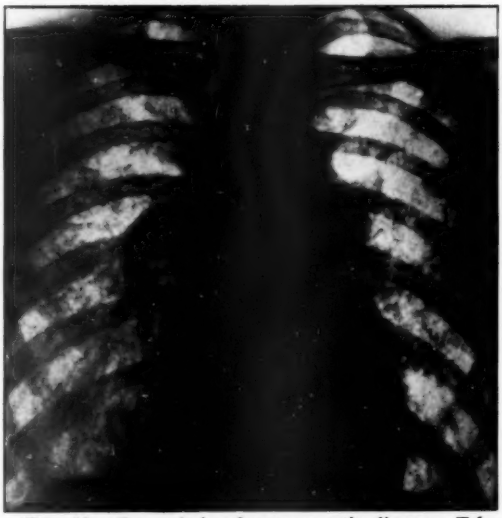


FIG. 13.—Congenital pulmonary cystic disease. Teleradiogram showing moderate enlargement of right heart and pulmonary arteries, and honeycomb appearance of lungs.

gestion (Fig. 13). He failed to respond to orthodox treatment which included a low sodium diet, digitalis, mercurial diuretics, and oxygen. He died suddenly on the day he had arranged to leave hospital.

At necropsy there was enlargement of the right heart and of the pulmonary artery. The customary signs of heart failure were present. Pulmonary cystic disease was a noticeable feature which has been described in greater detail by Cunningham and Parkinson (1950). In some parts of the lungs the smaller pulmonary branches showed partial or complete occlusion by endarteritis fibrosa and here and there aplasia or hypoplasia of the media.

Emphysema.—Mention has already been made of the necessity of allocating patients suffering from emphysema to one of two groups, the one carrying a favourable prognosis as a rule, and the other with an unfavourable outlook. This allocation has been made in a series of patients on two premises, clinical and pathological, and the variation shown by the two groups will now be discussed in relation to each.

Clinical features: The aim of clinical examination in a patient with emphysema is to discover the presence of heart failure. That this complication is rare in emphysema was emphasized by Parkinson and Hoyle (1937) who found it in only 13 of their 80 patients, although it was sought carefully during a period of two to three years.

Breathlessness, even at rest, is common to both groups. *Œdema*, invariable in the presence of heart failure, is not uncommon in elderly subjects with emphysema and without failure. *Ascites* is evidence of failure, but even in the rare group with heart failure it does not appear until a late phase of the illness. *Cyanosis* always accompanies pulmonary arterial obstruction which has produced pulmonary hypertension and heart failure, but it also occurs in patients with emphysema who are free from the complication of heart failure; it is sometimes explained by the presence of intra-alveolar hæmorrhage, and this is the usual cause of severe cyanosis in patients in this group. *Distension of neck veins* and a *rise in the right ventricular* and *pulmonary arterial pressure* are expected findings in emphysema complicated by heart failure, but the measure of each of these cannot by itself determine to which group many patients belong. It is difficult to decide in a case of emphysema whether the *liver* is distended from heart failure or dislodged downwards by the ballooned lungs. The *pulse* is small and the *blood pressure* is low in patients in whom heart failure has set in. *Right heart preponderance* may show in the electrocardiogram of each group, although the evidence is less in patients without failure (Fig. 14). On cardioscopy *slight cardiac enlargement* and *prominent hilar markings* are expected in the more innocent group (Fig. 15), while moderate or greater enlargement of the heart together with pulmonary congestion are features of the patient where heart failure has resulted (Fig. 16); the difficulty here is to distinguish the shadows made by natural pulmonary vessels rendered more discernible by excessively aerated

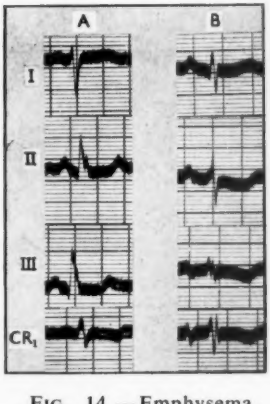
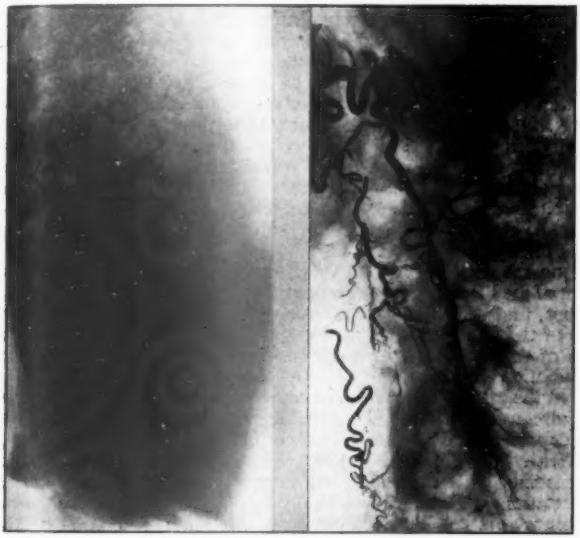


FIG. 14.—Emphysema. Electrocardiogram showing moderate right heart preponderance in absence of heart failure (A), and greater preponderance in patient with failure (B).

FIG. 15.—Emphysema without heart failure. Teleradiogram showing no cardiac enlargement, prominent hilar markings, but no pulmonary congestion.

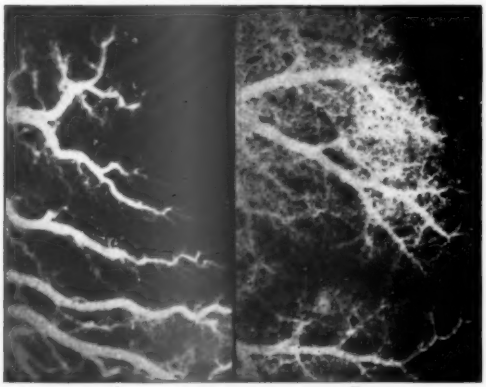
FIG. 16.—Emphysema with heart failure. Teleradiogram showing moderate right heart enlargement and pulmonary congestion.

lungs from those which are the outcome of congested pulmonary vessels. In the search for evidence of heart failure in the present series, special care was taken to discover a *triple rhythm* from addition of the third heart sound, for its presence in a patient over 40 years of age presumed more certainly than any other physical sign that heart failure had set in. If auscultation finds two heart sounds or dual rhythm, heart failure is not a complication.



A B

FIG. 17.—Emphysema. Bronchial arteriogram showing normal vessels in patient without heart failure (A), and exaggerated vessels in patient with heart failure (B).



A B

FIG. 18.—Emphysema. Pulmonary arteriogram showing pruning effect of terminal branches in patient with pulmonary hypertension and heart failure (A), and compared with normal control (B).

Pathological features: In patients with emphysema coming to necropsy the lungs were examined in the same special way as for cases of pulmonary hypertension. A radiogram taken after injection of a radio-opaque material into the bronchial arteries showed that their calibre was somewhat increased in the group showing heart failure, although not invariably, and the same changes have been seen in cases with heavy pulmonary infection; radicles of the pulmonary artery were occasionally seen because of the entry of the injected material through the exaggerated natural fistulous openings (Fig. 17). Of greater value in the investigation of such cases has been the injection of the pulmonary artery, for when the smaller muscular arteries become obstructed by endarteritis fibrosa the radiogram demonstrates a pruning of the terminal branches of the pulmonary tree giving it an appearance of a denuded shrub in winter contrasting with the leafy bush in spring which typifies the healthy pulmonary circulation (Fig. 18). Shillingford (1950) has recently found this to be a guide to the subsequent histological investigation of the lesser arteries. Microscopy was directed specially to finding endarteritis fibrosa of the smaller arteries, aplasia or hypoplasia of their walls, sclerosis of veins, intra-alveolar hæmorrhage, bronchopneumonia, and the extent of the emphysema.

In 5 patients where emphysema was associated with heart failure the pathological investigation showed endarteritis fibrosa in the smaller muscular arteries obstructing in part or completely the lumen of many; connected with areas where this change was predominant were foci of aplasia and hypoplasia of the media. On the other hand in patients with emphysema and without heart failure, this change was usually missing, and, if present,

it was always minimal. Such patients survived emphysema for many years under the handicap of breathlessness and recurrent bouts of bronchitis; bronchopneumonia supervened ultimately and sometimes with conspicuous cyanosis from intra-alveolar hæmorrhage.

The manner of death in pulmonary emphysema has not always been reflected accurately through the years at casual necropsies. Too often a combination of emphysema, enlargement of the right heart and a certain degree of congestion of the liver and other organs has drawn the inference that death has resulted from heart failure. In fact, bronchopneumonia often superimposed on severe anoxæmia, explains the mechanism which leads to cardiac defeat in the large majority of patients with emphysema. In the rarer group where demise is the direct result of heart failure, a detailed examination of the state of the lesser pulmonary arteries at necropsy shows that obstruction within these by endarteritis fibrosa more than any other factor, like reduction of the capillary bed or oxygen-want, determines the conspicuous rise in pulmonary arterial pressure which in its turn causes heart failure. Clinically the presence of triple heart rhythm decides which group claims the patient. In every case of emphysema, therefore, we must listen attentively for this auscultatory sign at the lower end of the sternum with the patient in the reclining posture; should it be absent we may dispense reassurance and encouragement to the patient for he will last as long as bronchopneumonia stays away; if triple rhythm is present we should inform the relatives of the gravity of the illness because there is no turning it back.

Experience has impressed on me the necessity, in the investigation of pulmonary heart disease, of taking a radiogram of the lungs after injection of the pulmonary artery at necropsy with a radio-opaque substance, and of resorting to a close examination of at least a dozen sections of selected portions of the pulmonary circulation at its periphery, suitably stained to portray the elastic layers of the media of the lesser muscular arteries, and sometimes entailing a scrutiny of serial sections.

In summary I would say that the cause of obdurate pulmonary hypertension is inseparable from obstruction within the pulmonary arteries, and in man this results rarely from thrombosis in the main arteries, or from deposits of carcinomatous cells or bilharzia in the lesser arteries, but principally from endarteritis fibrosa of the smaller pulmonary arteries formed over inherent deficiencies of their medial coats. Thus, repetitive coughing as in primary pulmonary hypertension, congenital dilatation of the pulmonary artery, patent ductus arteriosus, auricular septal defect, pulmonary cystic disease, emphysema, and possibly mitral stenosis, are conditions which separately induce a degree of pulmonary hypertension, but in the presence of intact pulmonary arteries, it is not severe enough to affect adversely the course of the individual illness. On the other hand, should slight or moderate pulmonary hypertension initiated by these separate clinical states be taking place in the presence of inherent deficiencies in the walls of small pulmonary arteries, endarteritis fibrosa results and produces arterial obstruction which increases the hypertension sufficiently to cause heart failure, leading to an early demise of the patient and which characteristically happens suddenly. This mechanism, which is considered here to be common to the six clinical states that have been discussed, justifies their inclusion under the caption of *congenital pulmonary hypertension*. The clinical sign which by itself can assuredly predict this ominous progress is triple heart rhythm. Eager watch for this sign must, therefore, be our constant care, for its presence means that our vigil is soon to end.

I wish to acknowledge my indebtedness to those who have helped me in this work. Dr. Wilfred Stokes prepared bronchial arteriograms in patients with emphysema and Dr. John Shillingford the pulmonary arteriograms in more recent cases. Professor Dorothy Russell of the Bernhard Baron Institute of Pathology, London Hospital, has given freely of her help and so has Dr. W. W. Woods. I am especially grateful to Dr. J. R. Gilmour for his careful pathological reports on ten patients with emphysema at Oldchurch Hospital.

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Section of Surgery

President—Sir STANFORD CADE, K.B.E., C.B., F.R.C.S.

[*January* 3, 1951]

Birthmarks and Moles

By D. N. MATTHEWS, O.B.E., M.D., M.Ch., F.R.C.S.

Nature of the lesions.—The origin and the precise nature of these two commonplace lesions have given rise to much controversy. At first described as neoplasms it soon became evident that both differed in several respects from the generally accepted features of these tumours. For example the majority of birthmarks are congenital; proof is more difficult with moles, but it is not improbable that most of these are also present at birth. Neither has a capsule. Growth is often limitless whilst occasionally spontaneous disappearance occurs. These are some of the facts which raised the controversy, and further knowledge may yet alter the present-day opinions.

(*a*) *Birthmarks.*—These are now regarded as congenital malformations made up of ectopic rests of mesodermal vasoformative tissue [1]. This tissue is at first solid and consists of endothelial cells similar to those which line the blood vessels, interspaced with strands of connective tissue (Fig. 1). Later it becomes canalized and differentiated in varying degree so that a variety of clinical forms appears.

(*b*) *Moles.*—These lesions are made up of nævus cells derived from the stratum germinativum of the epithelium. The term "nævus" should therefore be restricted to the lesions formed from these cells, but in view of the common clinical practice of referring to birthmarks as "nævi" insistence on this would only add to the confusion of nomenclature. It was for this reason that the less scientific terms "Birthmark and Mole" were chosen for this paper.

Clusters of nævus cells arise and grow upwards towards the surface, or downwards into the dermis penetrating the membrane which separates it from the epidermis (Fig. 2). The amount of pigment which forms in these cells is very variable; sometimes none is present.

I. Birthmarks

Natural History

(1) *Differentiation.*—When canalization occurs recognizable arteries, veins and capillaries appear (Fig. 3). All three elements can be found in every lesion but one usually predominates and gives the birthmark its clinical characteristics. If two are present in large amounts the commonest combination is a mixture of cavernous and capillary tissue.

(2) *Complexity.*—Vasoformative cells are often intermingled with other mesodermal tissues which are themselves present in excessive amount. Fibromatous and lipomatous tissue is frequently found (Fig. 4); myomatous, chondromatous and osseous less often.

(3) *Vascularity.*—The rate of circulation through a capillary lesion is very slow and the blood pressure is so low that ulceration or trauma causes little bleeding; much less than from normal skin or granulation tissue. The slight hæmorrhage which does occur is easily controlled by pressure. Cavernous and arterial lesions, however, can bleed very fiercely. Cavernous birthmarks have extensive communications with the underlying systemic veins, and arterial vasoformative collections have a blood pressure equal to or closely approximating to that in the systemic vessels supplying them. It is not precisely known whether the increasing vascularity often seen in cavernous and arterial lesions is due to the acquisition of new communications with the systemic system by the cell mass, or to dilatation of pre-existing ones. There is, however, some evidence to support the view that the former process does occur.

(4) *Infection.*—Rapid growth of vasoformative tissue in the superficial layers of the epithelium may cause atrophy and ulceration of the skin (Fig. 5). In this event the whole area becomes infected including the surrounding normal tissues, in which an acute inflammatory reaction appears (Fig. 6). The ulcer heals very slowly with the formation of sufficient fibrous tissue to cause the disappearance of the birthmark except for a thin peripheral ring where, presumably, the blood supply from the surrounding skin is sufficient to allow it to survive (Fig. 7). The central healed area is usually normal enough in appearance to be cosmetically acceptable.

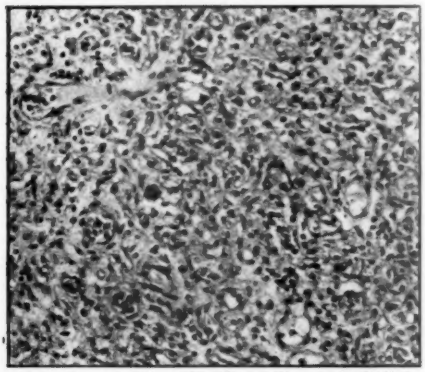

FIG. 1.—× 84. Vasoformative endothelial tissue.

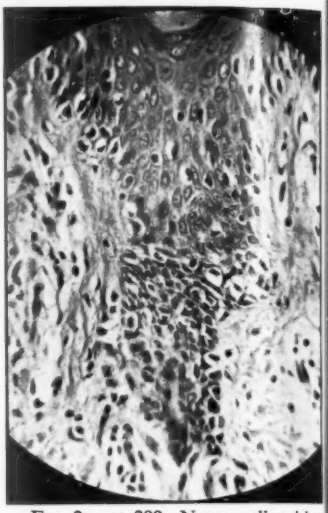

FIG. 2.—× 200. Nævus cells arising from the stratum germinativum and bursting downwards into the dermis.

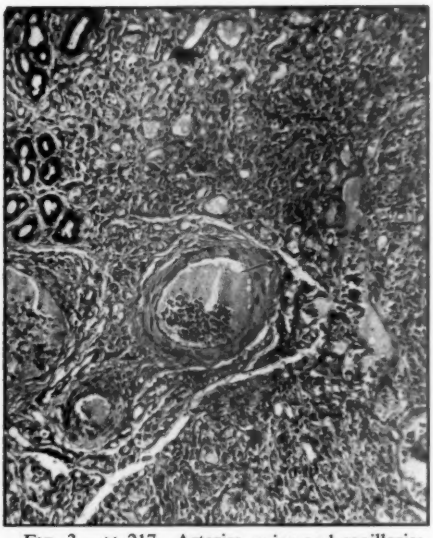

FIG. 3.—× 217. Arteries, veins and capillaries forming in vasoformative tissue. Glandular tissue in top left hand corner.

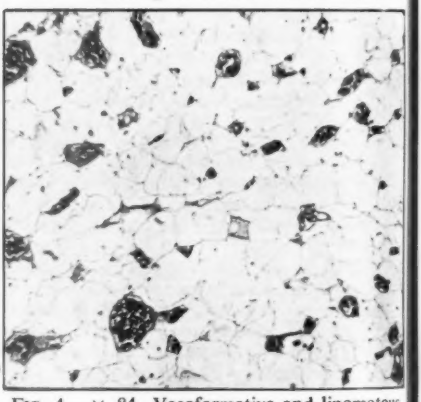

FIG. 4.—× 84. Vasoformative and lipomatous tissue in hæmangio-lipoma.

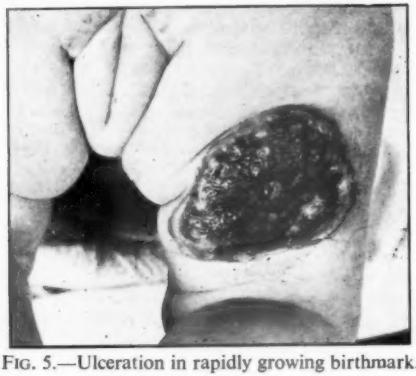

FIG. 5.—Ulceration in rapidly growing birthmark.

(5) *Hyperkeratosis.*—Gradual superficial extension of a vasoformative mass sometimes evokes a hyperkeratosis of the stratum corneum. This results in the formation of hard, raised nodules scattered over the surface of the birthmark (Fig. 8).

(6) *Infarction.*—It is well known that some birthmarks fade until they are no longer visible and shrink at the same time, leaving no deformity. This effect is produced by infarction and subsequent fibrosis. In some lesions, notably those at the glabella and the nape of the neck in the newborn, this is due to slowing and gradual failure of the circulation through tissue only poorly canalized [2]. There may be other factors, at present unknown, concerned in the shrinkage of larger lesions in older children.

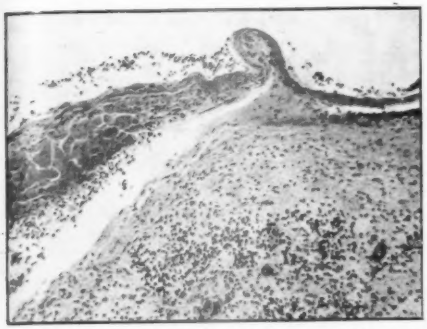

FIG. 6.—× 83. Infected and ulcerated birthmark with crust overlying it.

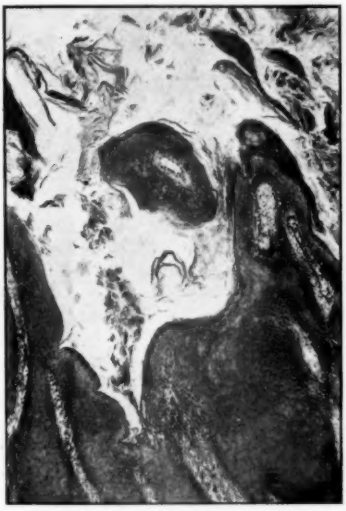

FIG. 8.—× 34. Hyperkeratotic reaction to underlying birthmark.

FIG. 7.—Typical result of ulceration of birthmark. Central thin white scar with residual peripheral ring of vasoformative tissue.

(7) *Growth and disappearance.*—Vasoformative tissue is capable of growth by the budding of new cells. It is also capable of increasing in size by the canalization of pre-existing solid tissue. It is not certain which plays the greater part and it is probable that both contribute in most lesions. The sudden dramatic increase in size which often occurs suggests the opening up of pre-existing tissue. But if all growth were due to canalization of pre-existing cells one would expect a very high incidence of peripheral recurrence after excision of a visible and palpable mass. In fact, this rarely if ever occurs if the edges are skirted by only a few millimetres. It is reasonable, therefore, to assume that the ability of such a lesion to grow is largely due to its power to bud new cells.

There is still much controversy regarding the frequency with which birthmarks disappear spontaneously. The problem arises because it is well known that they are commoner in children than in adults. Many workers have sought a solution by sending questionnaires to patients previously seen and documented. Lister [3], Bowers [4], and Walter [5], are all impressed with the high percentage of spontaneous cures whilst Pfahler [6], and Watson and McCarthy [1], amongst others, are entirely unconvinced. Pfahler states that he has never seen spontaneous disappearance whilst Watson and McCarthy record only 3 cases out of a series of 1,056. Those who believe there is a high incidence of spontaneous cure are in agreement that this is more likely to occur in the cavernous than the capillary type.

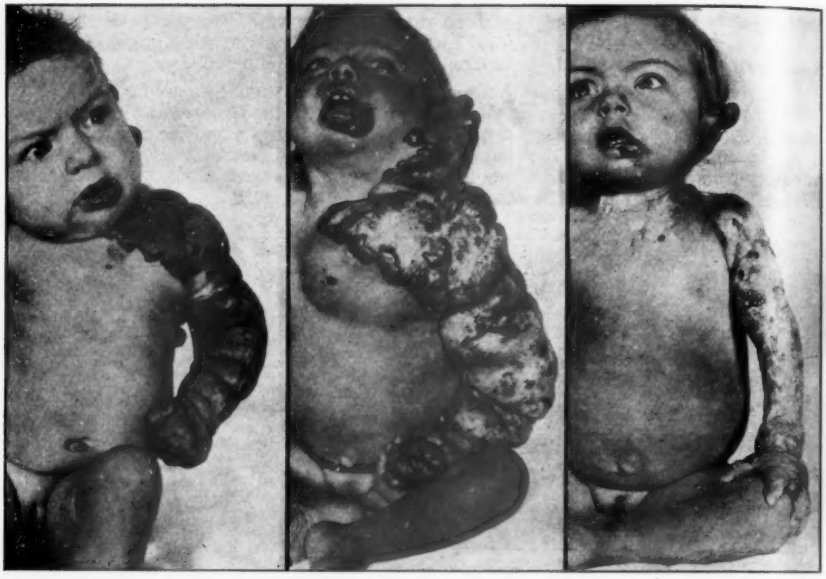

FIG. 9.—Cavernous hæmangioma growing rapidly: A, At two months. B, At eight months. C, After excision and grafting at one year. The function of the limb is normal.

As a surgeon one cannot help being impressed by the large number of lesions which do not disappear, by the number which grow rapidly and by the diversity of their structure and clinical form. It is not unlikely that all types can and sometimes do regress spontaneously but it is equally true that all types can grow rapidly. In my view the two which grow most rapidly and with the most serious consequences are the mixed caverno-capillary with large venous communications, and the bright red strawberry marks which often start as a single slightly raised small red spot (Fig. 9A, B, C). Both these may reach giant proportions in a short while and extend so widely as to become inoperable; they can then cause death from hæmorrhage, invasion of vital structures or cardiac damage. Capillary port-wine stains are also known to persist although they rarely increase dramatically in size or show a tendency to invade deeply. I do not think a pulsatile arterial birthmark ever regresses spontaneously. In my experience small, pale, flat, capillary lesions in the skin and small compressible subcutaneous cavernous lesions on the scalp are the most likely to regress, but it is my impression that even in these groups regression rarely occurs in children over 7.

CLINICAL CLASSIFICATION

Whilst all birthmarks are basically the same in that they are derived from vasoformative tissue it is not surprising that their clinical appearances are diverse, considering the variations in type, depth, site, and rate of growth, vascularization and canalization. When the pathological accidents of infection, infarction, thrombosis and fibrosis are added to this list of variables, it is amazing that the clinical pattern repeats itself often enough for any useful classification to be made.

The following classification includes the lesions commonly met in practice:

(1) *Spider nævus.*—This consists of a central mass of endothelial cells with capillaries radiating from it. It may not be clinically apparent at birth; it grows slowly and may regress spontaneously (Fig. 10).

(2) *Neonatal staining.*—This appears at birth as a small, flat, pink lesion on the head or neck. The glabellar and nuchal regions are the commonest sites. It consists of a thin layer of endothelial tissue in the skin. Canalization is slight and circulation through it is slow. It always disappears in a few months. The most likely explanation of its occurrence and subsequent disappearance is that blood is driven into it by the pressure exerted on the head at parturition but that when this is relaxed the circulation gradually fails again and thrombosis causes infarction and fibrosis.

(3) *Superficial capillary hæmangioma.*—(*a*) Salmon patch: This is a flat, pink lesion in

the skin. It occurs more commonly on the head and neck than elsewhere. It is often extensive and blanches with pressure. This type rarely grows dramatically and may fade completely in childhood (Fig. 11).

(*b*) *Port-wine stain*: This merits differentiation from the above group since it is different in behaviour and appearance although similar in structure. It consists of a thin layer of capillary tissue situated in the dermis. Circulation through it is poor. It is mauve and,

FIG. 10.

FIG. 11.

FIG. 13.

FIG. 12A.

FIG. 12B.

FIG. 10.—Spider nævus. FIG. 11.—Capillary hæmangioma. Salmon patch. Pale pink and flat.

FIG. 12.—Capillary hæmangioma. Port-wine stain with nodular surface: A, Before treatment. B, After excision in stages, and replacement by free skin grafts.

FIG. 13.—Capillary hæmangioma. Strawberry mark. Bright red and slightly raised.

although flat, frequently has several small hyperkeratotic nodules on its surface. It rarely if ever fades but grows with the child to persist in the adult without further enlargement (Fig. 12*a*, *b*).

(*c*) *Strawberry mark*: This is bright red, lobulated, and raised above the surface. It frequently starts as a single lobule and often grows with dramatic rapidity. Extensions may appear in the skin as outriders, separate from the main mass and later become incorporated with it. It invades deeply and is therefore potentially dangerous since it can readily become inoperable (Fig. 13). Despite these characteristics circulation through it is comparatively slow and the blood pressure is low. Ulceration of the overlying skin often occurs but hæmo-

rrhage is rarely severe. Fibrosis from the inevitable infection which follows, may bring about regression or cure. This lesion occurs with greater frequency on the limbs and trunk than the salmon patch or the port-wine stain.

(4) *Cavernous hæmangioma.*—This is a raised swelling which is soft and partly compressible. Capillary and arterial elements can be found in it but cavernous tissue predominates. When the blood is squeezed from it solid vasoformative tissue can be felt in variable amount. When the pressure is released the tumour swells up again as the blood flows back into the large venous spaces which compose it. A capillary strawberry mark is not infrequently

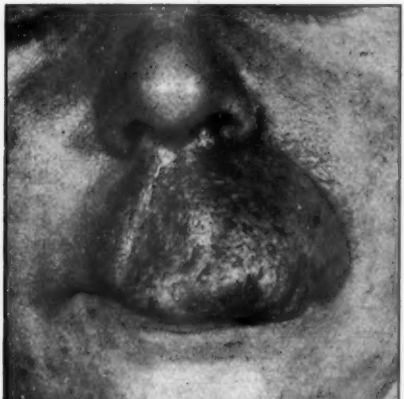

FIG. 14A.

FIG. 14B.

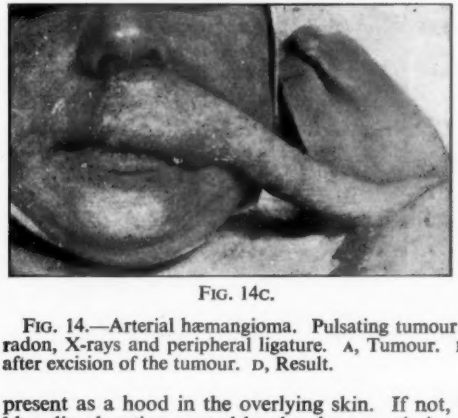

FIG. 14C.

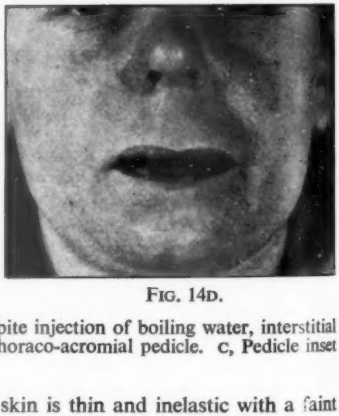

FIG. 14D.

FIG. 14.—Arterial hæmangioma. Pulsating tumour despite injection of boiling water, interstitial radon, X-rays and peripheral ligature. A, Tumour. B, Thoraco-acromial pedicle. C, Pedicle inset after excision of the tumour. D, Result.

present as a hood in the overlying skin. If not, the skin is thin and inelastic with a faint blue discoloration caused by the close proximity of the blood beneath. Hæmorrhage from trauma can be torrential since there is often extensive communication with the systemic veins. Whilst it is true that small lesions of this type on the scalp can regress, the majority, in my experience, persist and some grow relentlessly with occasional sudden dramatic increases in size as further vascularization occurs. The lip and cheek are common sites for these lesions and despite their softness they always profoundly affect the shape and size of the underlying bones. The eruption of the teeth is interfered with and the alveoli so distorted that there is gross malocclusion on the affected side. There is no justification in refraining from treating these cases in the hope that the lesion may ultimately regress (*see* Figs. 9 and 20).

(5) *Arterial hæmangioma.*—This consists of a pulsating tumour in which the tortuous nature of the vascular channels is demonstrated by the twisting of the vessels as the blood is driven through them. It is not a cirsoid aneurysm since it does not consist of a dilatation

of pre-existing vessels, although it may easily be mistaken for this when it occurs on the face. It may grow rapidly even in a young baby and when surface erosion occurs spurts of blood come from it and require immediate control by digital pressure. A cavernous element is sometimes combined with it, in which case it is possible to discern both the steady filling of the venous spaces and the return of arterial pulsation on release of pressure on the mass (Fig. 14).

(6) *Diffuse hæmangiomatous giantism.*—This is a condition in which a part of the body is hypertrophied as the result of widespread capillary lesions in it. It usually occurs in a limb when the ectopic vasoformative tissue can be demonstrated in all its components, including bone. The limb is increased in length as well as girth since the increased blood supply causes an overgrowth of all tissues (Fig. 15). There is such a large arteriovenous anastomosis through the vast capillary bed that right-sided heart failure may be precipitated unless high ligature of the main vessels or even amputation is undertaken in time. The limb is hot and may be painful. In my experience there is usually a lymphangiomatous element present as well, with gross enlargement of the lymphatic vessels.

(7) *Multiple familial telangiectases.*—This is rare but merits inclusion because it is a well-defined clinical entity and may on occasion present difficulty in diagnosis. It consists of multiple small capillary hæmangiomata affecting chiefly the mucous linings of the nose, throat and stomach. But lesions are also found in the parenchyma of the lung and in other viscera. There are nearly always a few small spider nævi on the skin. Attention is often drawn to the condition by spontaneous hæmorrhages from mucosal surfaces in middle life; it may reveal itself as an epistaxis, a hæmatemesis or a hæmoptysis. The multiple lesions in the stomach are often referred to as purpura of the stomach although the condition has nothing to do with thrombocytopenic purpura. The familial incidence of the condition is usually well marked.

Treatment

Indications

(1) *Hæmorrhage.*—Its prevention or arrest. Emergency treatment may be required to stop bleeding resulting from injury to, or ulceration of, a cavernous or an arterial hæmangioma. More rarely it may be needed after similar accidents to a capillary strawberry mark. Treatment is sometimes indicated to forestall a likely hæmorrhage in a cavernous or an arterial lesion where the overlying skin is thin. Treatment is also occasionally called for to arrest hæmorrhage from mucosal surfaces in familial telangiectases.

(2) *Ulceration.*—This complication will necessitate careful daily treatment until the ulcer has healed. This may take many weeks.

(3) *Growth.*—This is one of the most important indications for treatment and demands immediate action as soon as the lesion is seen to be extending. This applies particularly to young babies in whom the rapidity of growth is often such that even a short delay may be sufficient to allow the tumour to infiltrate very widely.

(4) *Disfigurement.*—This is probably the commonest indication for treatment at all ages. It is certainly the commonest in adults who seek relief from social embarrassment and psychological handicap. The frequency with which birthmarks occur on the face and their preponderance in females in a ratio of 3–1 make this readily understandable.

Methods of Treatment

(1) To sclerose the mass of vasoformative tissue, producing thrombosis in the canalized parts and devascularization of the whole lesion by the production of scar tissue.

(2) To remove the whole vasoformative mass, canalised and solid.

(3) To combine both the above methods.

Sclerosing Agents

Innumerable methods have been advocated to sclerose birthmarks and individual preference can be freely indulged. Some methods, however, are known to be risky and others to be relatively unsuccessful. The list given here includes the majority of methods in common use and the views expressed about each are necessarily personal.

(*a*) *Heat*	(i) Cautery. (ii) Diathermy.
(*b*) *Cold*	Carbon dioxide snow.
(*c*) *Irradiation*	(i) Surface radium (beta radiation). (ii) Interstitial radium (radon seeds and radium needles). (iii) X-rays. (iv) Radio-active paints (thorium-X).
(*d*) *Injection of irritant fluids* ..	(i) Boiling water. (ii) Saturated saline (33%). (iii) Ethamolin froth.

(*a*) *Heat.*—I prefer the diathermy to the cautery since with the latter there is always the risk of a red hot end accidentally falling on or touching the patient. Moreover with the diathermy it is possible to introduce the needle before turning on the current so that uniform heat is delivered to the full depth of the lesion when required. I believe that a spider nævus is best dealt with in this way. The whole of the vasoformative core is first sclerosed through a single puncture and then the skin is lightly touched with the needle point over the radiating venules without penetrating it. The single central puncture does not leave a visible scar.

Diathermy is also useful for treating some superficial capillary nævi, particularly where these are too extensive for the use of a beta radium plaque or are in a difficult position (Fig. 16). It is not satisfactory for port-wine stains but is helpful in large, flat salmon patch

FIG. 15.

FIG. 16A.

FIG. 16B.

FIG. 15.—Hæmangiomatous giantism. Leg is longer, fatter and warmer than its fellow. (Patient subsequently treated for me by Professor Sir James Paterson Ross.)

FIG. 16.—Diathermy coagulation to surface of capillary hæmangioma. A, Before treatment B, Result.

lesions and for tidying up any residual blemishes in raised strawberry marks not cured by injection treatment. When used for extensive capillary nævi the diathermy point must not penetrate the skin or it will leave unsightly scarring of the area. Instead, the entire surface of the lesion should be fulgurated by sparking the current as individual pin points set very close to each other. A general anæsthetic is needed and it is advisable to have more than one sitting for a large birthmark since it is painful for forty-eight hours post-operatively, and time consuming and tedious for the operator. The same area will often have to be fulgurated more than once but a minimum of two months should be allowed to elapse before this is done. The beneficial result of diathermy is slow to appear and it is very easy to overtreat the skin by not waiting long enough. This may produce a hypertrophic scar, as ugly as the original birthmark (Fig. 17).

(*b*) *Cold.*—Carbon dioxide snow has been used for many years in the treatment of birthmarks. Its usefulness is limited by its inability to act at a depth of more than one or two millimetres. It can, however, be used to treat flat capillary salmon patch lesions and spider nævi. The size of the applicator prevents its use for large lesions and some patients and parents complain of the circular ring of thin white skin which it often leaves. For this reason I prefer to use alternative methods even for small flat capillary lesions, although it is universally acknowledged that a perfect result can sometimes be achieved with it in such cases.

(*c*) *Irradiation.*—(i) *Surface radium*: The application of a beta radiation plaque is, in my opinion, the best way to treat a flat salmon patch capillary lesion except when this is so large that treatment would be inordinately protracted. Carefully used the plaque leaves no

FIG. 17A.

FIG. 17B.

FIG. 17, A and B.—Scarring caused by excessive diathermy coagulation of capillary hæmangioma.

FIG. 18A.

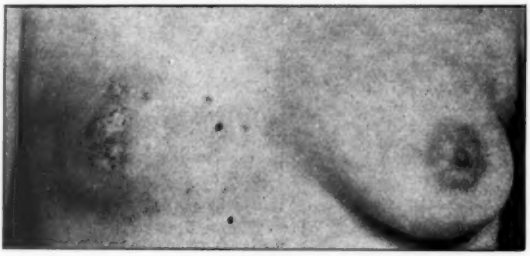

FIG. 18B.

FIG. 18.—Effects of radiation on growth of normal tissues. A, Under-development of lip following treatment of cavernous lesion with interstitial radon seeds in babyhood. B, Failure of breast and nipple to develop following treatment of capillary hæmangioma (strawberry mark) with radium needles.

mark at all. It has the great merit that its use does not frighten young children since it is small, light, easily applied and does not necessitate the child lying still. These facts justify its use even for comparatively large lesions on some occasions. The inability of beta rays to penetrate the tissues restricts the use of the plaque in the same way as carbon dioxide to superficial flat capillary lesions.

(ii and iii) *Interstitial radium and X-rays*: In my opinion the use of gamma rays either as radon, radium or X-rays is absolutely contraindicated for birthmarks except possibly for a very large infiltrating cavernous lesion. When operation is needed as a life-saving measure in such a case the very formidable operative risks can sometimes be reduced with justification in this way. The tragedies of treating benign birthmarks with gamma rays are not fully appreciated since the ill-effects may not become apparent for many years. The growth of normal surrounding tissues is retarded in children and radiation dermatitis is unnecessarily risked at all ages. A growing epiphysis is especially easily damaged. (Figs. 18 A and B).

(iv) *Radio-active paints*: I have no personal experience of the use of these substances

which deliver beta rays. They are used in the treatment of flat superficial lesions and I understand that the results are variable but on occasion very good [4].

(*d*) *Injection of irritant fluids.*—(i) *Boiling water*: The possibility of serious accident from spilling this on the patient absolutely precludes its use in my view. Since the lesion under treatment is usually on the face such an accident is a tragedy. The amount of sclerosis produced by boiling water is, moreover, variable and unpredictable which is an additional contra-indication to its use.

(ii) *Saturated saline*: This is an excellent sclerosing agent (Fig. 19), but so powerful that if injected into the skin, or in too great a quantity immediately beneath it, will cause a

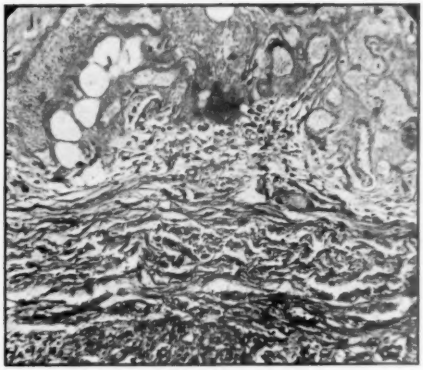

FIG. 19.—× 83. Sclerosis following injection of saturated saline. Upper half of field shows acellular, structureless, infarcted tissue with much collagen formation.

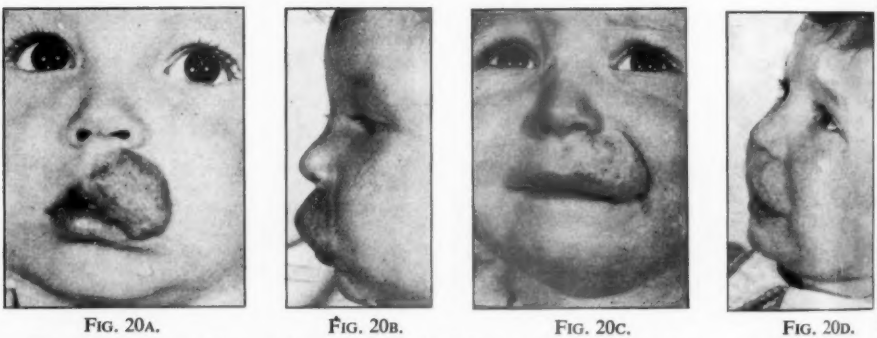

FIG. 20A. FIG. 20B. FIG. 20C. FIG. 20D.

FIG. 20.—Cavernous hæmangioma treated with injection of saturated saline. A and B, Before treatment. C and D, Result.

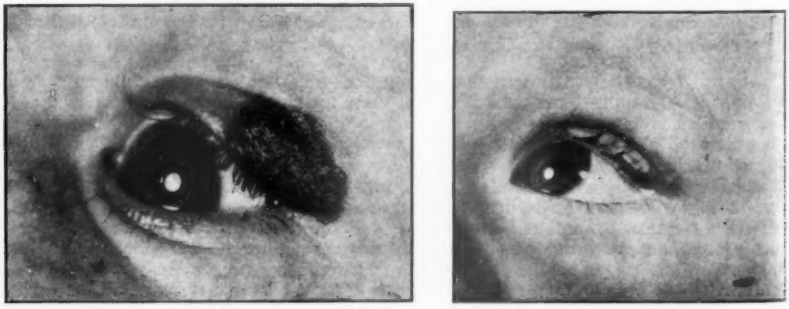

FIG. 21A. FIG. 21B.

FIG. 21.—Strawberry mark treated with saturated saline. A, Before treatment. B, Result.

slough. Its use was first suggested to me by Denis Browne [7]. Cavernous, mixed cavernous and capillary lesions and raised capillary strawberry marks can all be treated satisfactorily with it. Its power to shrink a large soft cavernous lesion is often dramatic and in so doing it usually takes the colour out of any overlying capillary skin blemish (Fig. 20). Its effect on the strawberry mark is also satisfactory (Fig. 21). A few small unfaded areas sometimes remain, however, and these are best dealt with by means of the diathermy or ethamolin.

The indications for the use of saturated saline are to shrink and fade such birthmarks when they are in areas where excision would be difficult or disfiguring, to lessen the magnitude of any surgery ultimately needed and to hold in check rapidly growing massive lesions until a baby is old enough to withstand major surgery. I have now treated over a hundred cases by the injection of saturated saline and the technique I employ is as follows.

The child attends the hospital as an outpatient. The average number of injections needed has been six. They are given at intervals of one month. Injection is made under general anæsthesia. A very fine (No. 20) needle is introduced obliquely through surrounding normal skin. The fluid is scattered in the depths of the lesion. No more than 0·2 ml. are injected at any one spot at one time. The total amount of fluid injected varies with the size of the lesion. The amount injected on each occasion in the case illustrated in Fig. 20 was 2 ml. and in Fig. 21 0·5 ml. On three occasions 15 ml. were given in an attempt to hold in check the lesion seen in Fig. 9. It was unsuccessful, doubtless on account of the vast communications with the venous system. Except in these large cavernous lesions penetration of a vessel by the needle is rare; the majority of injections are interstitial. When it does happen I have always welcomed the opportunity of injecting the saline intravascularly but I have not put more than 0·5 ml. into the vessel in a young baby for fear of convulsion; this has never occurred. After injection the lesion is compressed for twenty-four hours with a pad of gauze held with elastic adhesive tape. Compression appears to increase the sclerosis and it has recently been suggested to me by Truman Blocker [8] in America that it would be worth emptying the lesion first by sticking transparent adhesive tape over it and injecting through this under direct vision. There is considerable swelling for forty-eight hours after the injection but little pain is experienced.

The danger of sloughing the skin by injecting saturated saline into it is so great that repetition of the warning against doing so is justifiable.

The only serious disadvantage to the use of saturated saline is that children become apprehensive of visiting hospital when they know that an anæsthetic awaits them each time. This disadvantage is obviously outweighed when its use is restricted to the indications given above, but is sufficiently serious to contra-indicate its employment for small lesions in situations where they can be removed without causing disfigurement. It is also worth noting that the organization needed to treat large numbers of children as outpatients is considerable, since accommodation is required for them to rest after the anæsthetic.

(iii) *Ethamolin froth*: This is made by shaking 1 ml. of Ethamolin (or sodium morrhuate 5%) with an equal amount of air in a syringe. I used this in an endeavour to treat port-wine stains by the intradermal injection of minute quantities of a substance which, although an irritant, would not slough the skin. The results have been disappointing and I have abandoned the attempt; but Ethamolin froth has proved very satisfactory in the later stages of the injection treatment of strawberry marks, when final injections have been needed so close to the skin that I have been doubtful of the wisdom of using saturated saline. This substance often improves the result when injected intradermally in very small quantities. It does not slough the skin.

Surgery

Port-wine stains, arterial hæmangiomata and massive cavernous lesions need to be excised and the defects repaired. Hæmangiomatous giantism demands ligation of the appropriate vessels, and under the circumstances noted above some small lesions suitable for saline injection are also best treated surgically.

The method of repair will be determined by the amount and depth of the tissue excised. Thin port-wine stains should in my opinion be replaced by a comparably thin skin graft. The use of a skin flap for these lesions on the face robs it of its natural play of expression. The stain should be excised and grafted in stages at intervals of three months so that the boundaries of each graft fall into the natural lines of the face (*see* Fig. 12). If these are ignored and a single large graft is used, subsequent contraction may cause unsightly distortion. Where the full thickness of the lip or cheek has to be removed, a pedicle flap with an appropriate lining must be provided (Fig. 14).

II. Moles

Clinical Types

(1) *Flat.*—This is the commonest type of nævus cell lesion. The amount of pigment is variable and it is scattered diffusely in the nævus cells and in the stratum germinativum of the epidermis (Fig. 22). The lesions are often multiple and may be very extensive.

(2) *Hyperkeratotic.*—Upward growth of the nævus cells sometimes evokes a hypertrophic response in the stratum corneum similar to that seen in birthmarks (Figs. 23 and 25). The lesion then stands out from the skin as a series of pigmented nodules.

(3) *Hirsute.*—The association of thick tufts of hair with a mole is not uncommon (Fig. 24). The nævus cells are seen to be present in great profusion in these lesions surrounding the hair follicles. There is usually a great quantity of pigment in the cells of such moles.

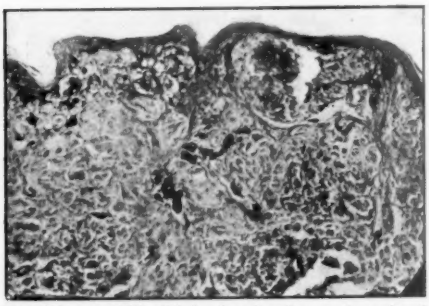

Fig. 22.—× 188. Mole showing heavy deposit of pigment in all layers.

Fig. 23.—× 34. Mole showing hyperkeratotic reaction.

Fig. 24.—Hirsutism in extensive deeply pigmented mole.

Natural History

(1) *Growth.*—After starting by comparatively rapid enlargement from a very small lesion, moles usually grow through childhood keeping pace with the growth of the part on which they are situated. They cease growing when adult life is reached but are liable after this to sudden rapid increases in size interspaced with periods of quiescence lasting many years. They do not regress spontaneously.

(2) *Malignancy.*—The clinical diagnosis of malignancy is difficult to make. An increase in size, friability, vascularity or pigmentation is not proof of malignancy, but merely that the mole is in a phase of activity. It is true that if malignancy occurs it is most likely to do so during such a phase but the only proof that it has taken place is cytological. This puts a

grave responsibility on the histologist who has to search the whole lesion most carefully. None the less, the appreciation of this point, whilst emphasizing the need for excision if activity is observed, gives hope that despite it the lesion may still be benign. Conversely, it emphasizes that the lesion may be malignant even in the absence of pigmentation or friability.

FIG. 26A.

FIG. 26B.

FIG. 27B.

FIG. 26.—Hairy pigmented mole treated by excision and replacement by free skin graft. A, Before, B, Two years after operation.

FIG. 27A, B, C.—Extensive mole under treatment by central skin grafts and repeated marginal excisions.

FIG. 27A.

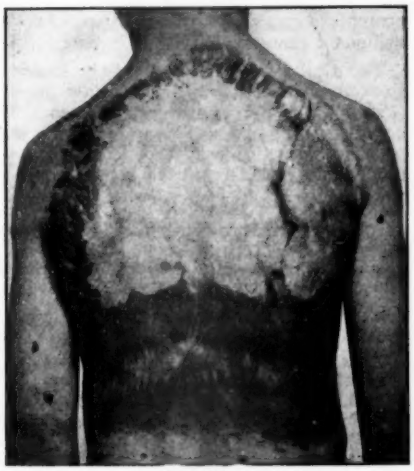

FIG. 27C.

FIG. 25A.

FIG. 25B.

FIG. 25.—Nodular formation on mole. Treated by excision and suture. A, Before, B After treatment.

The microscope has to decide. Malignancy is so rare before puberty that one is tempted to say that it never occurs whatever the clinical appearance may be.

(3) *Metastasis.*—The practical points with regard to the spread of a malignant mole are that it travels to the regional lymphatic nodes through the main lymphatic vessels, that it may form a chain of non-pigmented cutaneous seedlings along the line of these channels and that it tends to recur locally as a ring of similar seedlings an inch or two away from the site of the original tumour. This last fact suggests early invasion of the local tissues or cutaneous lymphatics and demands very wide excision of a mole when it is removed from an adult during a phase of activity.

TREATMENT

There is not, so far as I am aware, any method of treating moles other than by excision, nor is there any evidence that they disappear spontaneously. The principal indication for their removal in children is cosmetic, although fear of malignancy when the child is grown prompts some parents to seek treatment despite the known fact that the incidence of malignant change in adult life is very small.

The ideal form of treatment is by excision and suture (Fig. 25). But where the shape or size of the lesion does not permit this the surgeon has a choice between excision and grafting (Fig. 26), and partial excision repeated at three monthly intervals until the lesion has been completely removed. This procedure is quite safe in children and often provides the best solution cosmetically in large lesions. Sometimes the two methods can be advantageously combined by placing a graft centrally and removing surrounding pieces of the mole afterwards (Fig. 27).

I wish to record my thanks to Dr. Martin Bodian for his help in the preparation of the histological slides, and to record my indebtedness to Mr. Derek Martin and the Staff of the Photographic Department of the Hospital for Sick Children, and to Mr. Bligh and the Photographic Staff of University College Hospital for the illustrations.

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Neo-Natal Intestinal Obstruction

By Denis Browne, F.R.C.S.

There are certain requirements for the efficient treatment of small babies who suffer from some impediment to the normal passage of the intestinal contents:

(1) *A nursing staff* skilled in the difficult and most important task of feeding and tending these minute patients. They depend, to an extent far greater than those older and larger, upon continuous observation and immediate intelligent reaction to emergencies for their chances of survival. To give only two examples: it is extremely easy to give a baby a heat-stroke by wrapping it up in a blanket with an equal mass of hot water in a rubber bottle; and a newly born child will choke to death from an obstruction that in later life would be dealt with by a single cough.

(2) *An anæsthetist* trained in the particular technique involved. The keeping of a free airway and complete control of anæsthesia in a small baby is only possible by eliminating the obstruction of the glottis, which at that age is so liable to spasm, by holding it open with a soft rubber tube.

I believe that it is most important in difficult cases to keep the amount of anæsthetic as low as possible; that it is far better to have the anæsthetic so light that the child struggles slightly under the operation rather than so deep that it takes long to recover the power of coughing and crying, so aerating its blood and clearing its air passages. One manœuvre which I consider of great value in certain critical cases is what I call the "double induction". Supposing that after opening the abdomen the surgeon finds that a longish procedure such as a resection of gut is needed: he packs off the abdomen and asks the anæsthetist to stop all administration of anæsthetic. When the anastomosis is completed, he holds the bowel controlled by a swab, and asks for a second induction of the child to a depth that will permit closure of the peritoneum. With an intratracheal tube, and in a small exhausted infant, this is easily and rapidly obtained; so saving the absorption of the anæsthetic that otherwise would have been administered over half an hour or so. Success in operations on the newborn depends very largely on the understanding and confidence between surgeon and anæsthetist that are necessary for such teamwork. Speed and ease of operating bought at the cost of deep anæsthesia are also bought at the cost of danger to the child.

(3) *An operating equipment* suitable for the type of surgery that may be expected. It is merely necessary to ask the average operating theatre staff to set out a table for an anastomosis of the bowel in a newly born infant to see that instruments of the necessary fineness are simply not available. As a personal preference I like to do all my surgical sewing with needles of the curve used by Moynihan, that is to say of about two-thirds of a circle. Needles of the fineness necessary for the newborn bowel must of course be handled with a needle-holder, and the stock patterns show one of the curious deficiencies to be noticed in surgical instruments; which, as a general rule, are made by people ignorant of their use and used by people ignorant of their making. This fault is that the body of a curved needle is made round, so that it spins in the grip of a needle-holder, although it can be used satisfactorily in the fingers. For many years I have had fully curved minute needles made with flattened shafts, and have tried in vain to stop them being called "cleft palate" needles. Although their immunity from twisting in metal grips certainly makes them most efficient in cleft palate operations, it does not cease to be useful when other flimsy and inaccessible tissues are being sewn.

A retractor that will enable the surgeon to pull any piece of tissue in any direction which he may wish is indispensable to the surgeon who has once learnt to depend upon it: and the only form of lighting that will enable him to see into deep narrow clefts, that is to say a headlight, will probably come into general use when an efficient one does not have to be made up by the operator himself.

(4) *A surgeon* specially skilled and interested in such cases is the final and not unimportant requirement. These cases are few in number, technically difficult and of critical importance. When a department of surgery has these characteristics there is only one way of gaining efficiency in it; that is to concentrate it in certain special centres, possessing the four desiderata which I have set out. The average competent general surgeon will have no greater success with neonatal bowel obstructions than he would have with brain tumours.

Diagnosis

It may seem a platitude to say that the indications for operation on intestinal obstruction are the same at all ages. In the cases of these small babies, however, there is a grave tendency for a vicious circle to arise; and until it is broken results in general will not be good. It

arises from the natural dislike of the pædiatric physician, under whose care most of these cases first come, to subject such a very fragile patient to the severe operation of laparotomy. In consequence he postpones the calling in of a surgeon until it is obvious that "medical treatment" is going to lead to disaster. The surgeon is faced with a starved and exhausted baby, only too often hopelessly distended; and not infrequently has the mortification of finding in a moribund infant a condition that in itself could have been easily set right by surgery. If he protests to the physician he is met by the statement that the cases which are operated upon do very badly; and so the vicious circle proceeds. It should be recognized that small babies stand laparotomies very well while they are in good condition.

One simple and valuable means of investigation which is far too little used is the straight X-ray of the abdomen. In many cases this demonstrates with the utmost clearness a distended gas-filled loop of bowel, with a consequent need for urgent operation. Barium meals are of very limited usefulness, and in many conditions the adding of an insoluble mass of mineral to the other difficulties the bowel has to contend with is far from helpful.

Preparation for Operation

An intravenous drip should be invariably set up, to supply the fluid and food which are invariably lacking. Expert advice as to the state of blood chlorides and other biochemistry is necessary if the drip is to be kept running any time. Time, however, should not be wasted in trying to get the body chemistry right while neglecting to attack the condition which has set it wrong.

I think it is a great advantage to have the baby fastened to a cross of padded wood during operation. This enables the anæsthetic to be kept at a level which otherwise would need manual restraint, and also avoids the risk of undue chilling of exposed limbs.

Incision

I have come to the conclusion that a transverse incision across both recti muscles is distinctly better than the more usual paramedian or mid-line approach. For an equivalent length of cut it gives a wider exposure, and if mischief is found on one side or the other, it can be safely and rapidly extended into the loin. I have been struck on many occasions by the failure of explorations of the deep abdomen and the loin conducted through paramedian incisions, though it is long since Rutherford Morison demonstrated the advantage of transverse muscle-cutting ones.

Exploration

At one time I used to try to determine what was wrong without allowing the bowels to escape from the abdomen. I am convinced this was wrong, and that the speed and clarity of diagnosis permitted by a deliberate turning out of the whole mass of bowel far outweigh the possible shock it may cause. I think that the main factor in "surgical shock" is an overdose of anæsthetic, caused by insistence on complete relaxation and by keeping the patient too long on the operating table.

Technique of Bowel Anastomosis

It is, of course, impossible in a short paper to go into the methods of treating the various technical problems that may be found. There is one, however, that constantly confronts the surgeon, to which very little guidance can be obtained in textbooks of operative surgery. It is that of anastomosing a widely dilated blind end of the bowel to a correspondingly shrunken empty tube below it. The ordinary end-to-end, end-to-side, or side-to-side anastomoses are useless here: the ordinary technique of controlling the bowel by clamps is inapplicable. The best method I have found is as follows:

(*a*) Two holding stitches are inserted into the dilated blind end, about an inch apart on either side of its apex. By these the blind end is held up so that the gas in it rises to beneath where an incision some half-inch long is made between the holding stitches. When the gas has escaped a suction tube is inserted to empty the distended gut. An assistant can aid in this by cautiously "milking" the bowel towards the sucking orifice.

(*b*) When the blind end is empty an incision is made along the free edge of the empty bowel below, corresponding in length to the half-inch slit made above it. The two slits are then anastomosed together by means of a single row of fine silk mattress stitches. The double row of stitching of the conventional intestinal anastomosis is impossible to insert without unduly narrowing the minute lumen of the empty lower piece of bowel. An anastomosis of this kind enables the flow of intestinal contents to pass straight down the tube of bowel, without the eddies and backwaters that are inevitable in a side-to-side or end-to-end junction (Figs. 1 and 2).

Technique of Colostomy

In many varieties of imperforate anus, with or without high urethral or vaginal fistulæ, a colostomy is probably the best primary treatment. Usually this is made in the left inguinal region without a spur which has many disadvantages:

(*a*) The situation of the opening hinders access to the pelvis in any subsequent operations that may be attempted to give a normally working anus, and in addition anchors the pelvic colon, whence should come the extra length of bowel that is needed if the blind end is to be brought through the perineum without tension.

(*b*) The spurless colostomy is notoriously difficult to close.

(*c*) Such colostomies are particularly liable to large prolapses.

The most satisfactory method is to make a transverse skin incision between the umbilicus and the xiphisternum, and then to open the abdomen in the mid-line. Through this incision the abdomen is explored. A piece of rubber tubing is then passed through the mesentery of the transverse colon about its centre. While the bowel is held by the tubing a spur is formed in the ordinary way by fine sutures, and then the tubing followed by the loop is brought through a separate small incision splitting the left rectus, which has been exposed by the skin incision. This incision should be made on the small side at first, and enlarged to the exact dimensions the surgeon considers will give a suitable anal ring (Figs. 3 and 4). To be sure of the final size of this ring when the ordinary technique is used is very difficult.

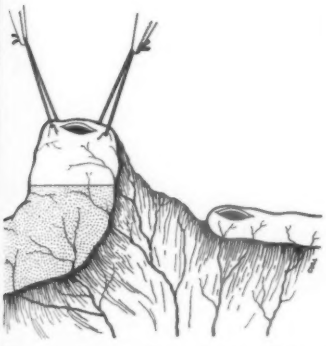

Fig. 1.—Preparation for the anastomosis of a blind end of bowel to a contracted segment below it. The dilated upper segment is shown held up by two sutures, with an incision between them through which the contents will be removed by suction. The empty segment has been incised along the free border of the bowel. Actually the contrast in size between the two segments is usually much greater than is shown in the figure.

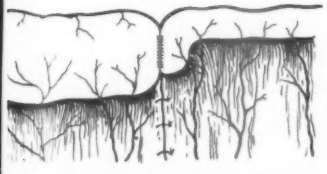

Fig. 2.—Stitching of the bowel shown in Fig. 1. The course of the intestinal flow is continued down the axis of the upper segment.

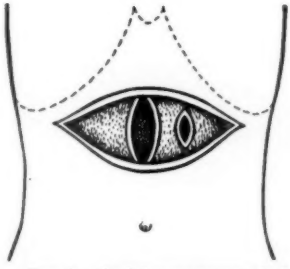

Fig. 3.—Incision recommended for colostomy. The skin cut is transverse. In the mid-line can be seen the longitudinal incision through which a laparotomy has been carried out. Through the left rectus there is a small incision which will just allow the double loop of transverse colon to be drawn through it.

Fig. 4.—Preparation of the transverse colon for a spur colostomy, to be drawn through the small incision shown in Fig. 3. When the colostomy is in its final position a plastic rod is thrust into one end of the rubber tubing shown, and so drawn through the loop to lie on the skin and prevent retraction.

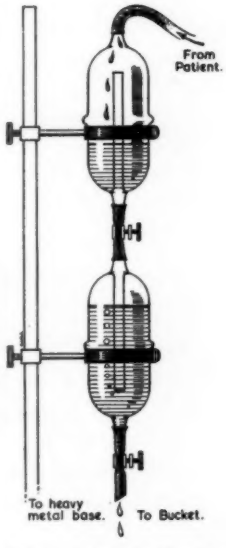

Fig. 5.—Diagram of suction apparatus recommended. The upper flask acts as a trap for extracted fluid, and the lower one supplies the suction by the tendency of its contents to run downwards.

The flasks can be arranged side by side.

AFTER-TREATMENT

Small babies upon whom a laparotomy has been performed should be kept on gastric suction by means of a Ryle's tube passed down the nostril until the bowel has begun working. This diminishes the risk of the child inhaling a sudden back-flooding of gastric and intestinal contents, and also much diminishes gaseous distension of the bowel with its consequent paralysis. There is no generally accepted neat and compact apparatus for gastro-duodenal suction, and it is difficult to avoid the conclusion that the lives of a good many patients of all ages are lost through failure to make use of this treatment. I have found that two large versions of the common dropper used in intravenous transfusions arranged one above the other with the inner tubes opening in opposite directions act very well. The lower "Suction flask", filled as necessary by disconnecting its upper end and running in water by a funnel inserted into the lower piece of tubing, supplies the suction and shows the passage of gas. The upper flask collects the fluid drawn off (Fig. 5).

[*February* 7, 1951]

The following specimens were shown:

(1) Ring Gallstones. (2) Adenoma of Suprarenal.—Mr. JOHN HOSFORD.

Pneumonectomy for Carcinoma of Lung. Death 10½ Years Later from Pneumonia, but No Recurrence.—Mr. IVOR LEWIS.

(1) Fibrosarcoma of Breast. (2) Leiomyomata of Bowel. (3) Synoviomata.—Dr. GEORGE LUMB.

Retrograde Jejuno-duodenal Intussusception.—Mr. T. LEVITT.

Disobliterative Endarteriectomy.—Mr. FRANK FORTY.

(1) Volvulus of the Stomach. (2) Partial Ametanephrogenesis.—Mr. R. H. GARDINER.

Specimens of Neurofibromata (Two of Vagus Nerve).—Mr. J. R. B. WILLIAMS.

Neurilemmoma of the Small Intestine.—Mr. H. H. G. EASTCOTT.

Two Cases of Neurofibrosarcoma of the Thigh.—Mr. D. L. B. FARLEY.

Carcinoma of the Common Bile Duct.—Mr. DAVID TIBBS.

(1) Sarcoma in Case of Paget's Disease. (2) Cystic Adenocarcinoma of the Pancreas.—Mr. P. G. LARGE.

Specimens Relating to a Case of Carcinoma of the Breast.—Mr. B. H. PAGE.

(1) Dermoid Cyst of Testicle. (2) Partial Hepatectomy for Tumour of Liver.—Mr. A. S. TILL.

Section of Anæsthetics

President—W. ALEXANDER LOW, M.C., M.B., B.S., F.F.A. R.C.S.

[*February* 2, 1951]

Problems of Developing Muscle-Relaxants in the Laboratory

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PROPERTIES REQUIRED OF RELAXANTS FOR CLINICAL USE

FOUR relaxants, which act by blocking the nerve-muscle junction, are already used clinically in this country. We cannot tell whether new relaxants are required, nor what properties would be particularly desirable in them, until we have answered the following questions:

(i) What properties does the clinician need?

(ii) How far do existing relaxants fulfil his requirements?

In Table I, I have tried to summarize the properties that are particularly important clinically.

TABLE I.—PROPERTIES REQUIRED OF MUSCLE-RELAXANTS FOR CLINICAL USE

(1) *Specificity of muscle-relaxant action.*
Adequate muscle-relaxation at doses not producing side-effects, such as:
- (*a*) Release of histamine
- (*b*) Block of sympathetic ganglia
- (*c*) Block of parasympathetic ganglia

(2) *Effects on respiration.*
- (*a*) Sparing: e.g. lower abdominal surgery, explorations requiring anæsthesia
- (*b*) Arresting: e.g. thoracic surgery

(3) *Duration of muscle-relaxant action.*
- (*a*) Short: e.g. intubation, explorations
- (*b*) Medium: e.g. shorter operations
- (*c*) Long: e.g. longer operations
- (*d*) Very long: e.g. spastic paralysis

(4) *Antagonism by reasonably safe substance.*

(5) *Relation to anæsthetics.*
- (*a*) Lack of serious antagonism between anæsthetic and relaxant
- (*b*) Suitability for mixture with intravenous anæsthetic

This table is largely based on discussions with members of this Section. They have made it clear that a property which suits one purpose may not necessarily suit another. For

example, a drug which relaxes muscles for only a few minutes might be best for intubation, while another substance, an equipotent dose of which lasts several times as long, would be more suitable for an abdominal operation.

The properties required of a relaxant for a particular operation will depend, too, on the background of anæsthetic and surgical technique to be used. Where, for instance, it is expected to ventilate the lungs artificially, the relaxant need not spare natural respiration.

It seems to be clear from Table I that a successful muscle-relaxant must combine a whole set of desirable properties. It is worth while attempting to outline very briefly how far existing muscle-relaxants exhibit some of these properties in man.

Gallamine triethiodide (Flaxedil) does not appear to block sympathetic ganglia at effective doses; but it does block parasympathetic ganglia, giving rise to the tachycardia recently described by Drs. Wylie and Doughty (1951). The figures published by these authors and by Unna *et al.* (1950*b*) suggest that gallamine spares respiration in man to a greater extent than tubocurarine or decamethonium.

Tubocurarine chloride is liable to produce each of the three side-effects given in Table I (*see* e.g. Grob, Lilienthal and Harvey, 1947). It acts for longer than other muscle-relaxants in equipotent doses.

Dimethyltubocurarine iodide has not yet been reported to produce in man side-effects similar to those of tubocurarine. According to Unna *et al.* (1950*a*) this compound spares respiration in volunteers more than the other three established relaxants.

Decamethonium iodide is free, at effective doses, of the side-effects which may accompany the other relaxants. An effective dose acts for a relatively short time. Decamethonium iodide is not antagonized by neostigmine; and it appears to be agreed that its antagonist—pentamethonium iodide—is not a safe drug to administer after surgical operations (*see* e.g. Davison, 1950). Unlike curare derivatives decamethonium iodide antagonizes ether (*see* Paton and Zaimis, 1950).

From the above summaries of their properties in man, it would seem that these four compounds represent a fairly satisfactory set for clinical use. However, as far as purely clinical needs go, niches would seem to exist for:

(i) A really short-acting relaxant, without the side-effects described, with sparing of respiration and preferably antagonized by neostigmine.

(ii) A relaxant acting for as long or longer than tubocurarine, but without liability to its side-effects, and antagonized by neostigmine.

Assessment of Muscle-relaxants in the Laboratory

I have put clinical requirements and their present state of fulfilment first because they are, in my opinion, the starting point from which one should attempt to develop in the laboratory new muscle-relaxant drugs. Our next problem is—what experiments in animals or on isolated animal tissues will tell us how far a new substance is likely to fulfil the needs of clinicians? The best way to answer this question is perhaps to consider first the established muscle-relaxants which I have already mentioned. We can then compare the results obtained with these drugs in animals with those obtained in man, both in volunteers and in patients. It will be most convenient to follow out this comparison under the heads given in Table I.

(1) *Specific Relaxant Activity*

From the point of view of its specific relaxant activity, a good compound is one in which the para[1]ysing dose is many times lower than the dose producing any undesirable side-effects.

If we want to try and assess this relationship in laboratory experiments, then we must measure both the dose which relaxes muscles and the doses which produce the various side-effects given in Table I. Each of these measurements presents its own problems. How are we to measure muscle-relaxant activity? And, what species of animals should we use?

(*a*) *Animal species to be used.*—I would like to limit the discussion of animal species to mammals. It is true that muscle-relaxant activity has been assessed in birds and amphibia, but I think it is *a priori* less likely that vertebrates of another class will indicate the probable activity of compounds in man.

In order to show how results may vary from species to species, I have given in Fig. 1 the relaxant activities of the four clinical drugs in relation to tubocurarine in 5 mammals. These figures are based on the publications of Collier and Hall, 1950; Collier *et al.*, 1948; Mushin *et al.*, 1949; Paton and Zaimis, 1949; Unna *et al.*, 1950*a*, 1950*b*; Wien, 1948.

Fig. 1 shows that the order of activities varies widely from mammal to mammal. The only animal which even places the drugs in the same order of activity as in man is the cat.

The rabbit does no more than put them in the same relation to tubocurarine as they stand in man. The rat and mouse are unduly insensitive to the synthetic compounds.

FIG. 1.—Log. potency of muscle-relaxants in various mammals in relation to tubocurarine in the rat (= 2·0). G = Gallamine triethiodide. T = Tubocurarine chloride. D = Dimethyltubocurarine iodide. C_{10} = Decamethonium iodide. The log. potency of gallamine triethiodide in the rat = 0·0 if that of tubocurarine = 2·0 (*see* Wien, 1948).

I think Fig. 1 shows that no laboratory animal can give an accurate forecast of the activity of a new compound in man. We certainly ought to make tests in the cat and rabbit, and, for good measure and because of its value in anæsthetic experiments, in the mouse.

(*b*) *Type of test to be used.*—Our next question is—what muscle or group of muscles ought we to use in our tests? Since generally, though not always, surgeons require relaxation of the abdominal body-wall, it might be thought that the musculature of this region would be the most desirable for tests in animals. Owing to technical difficulties, these muscles are not generally used in the laboratory. Longo and Bovet (1949) have, however, described a method of measuring intra-abdominal pressure in the rabbit; and they have compared by this means gallamine, tubocurarine and other drugs.

Most of the simpler and quicker tests at present in use depend on observing the failure of a group of muscles which usually work in co-ordination. Responses of this type which have been used include:

(i) Loss of righting reflex (Collier *et al.*, 1949*a*).

(ii) Loss of ability to hold on to a rotating surface or inclined plane (Skinner and Young, 1947; Allmark and Bachinski, 1949; Collier *et al.*, 1949*b*).

(iii) Head-drop in the rabbit (Dutta and MacIntosh, 1949).

Tests of types (i) and (ii) give a quantal response; and results can be expressed in terms of the 50% effective dose, or ED50. The head-drop test of Dutta and MacIntosh, which involves slow intravenous infusion of a drug solution, is in the nature of a titration; the end-point being the drop of the rabbit's head.

In my opinion tests of this type are exceedingly useful. They are rapid and simple, because they only involve intravenous injection, and they give a good idea of the capacity of a drug to relax important groups of skeletal muscles. But, of course, an animal may respond to other drugs than muscle-relaxants by losing its righting reflex or falling off a drum. So for this reason, and for others, results obtained with these simple tests must be checked in another way.

Preparations useful for this purpose can be made with the *tibialis*, *soleus* or other muscles of the cat. Since these muscles are not separated from the whole animal, and the blood flows to and from them normally, they can be used to show for how long a drug acts, and to compare the effect with that on respiration.

It is interesting that experiments with *soleus* and *tibialis*, performed by Paton and Zaimis (1950), show that the two muscles react differently to relaxants. *Tibialis* is relatively more sensitive to decamethonium than is *soleus*; but it is not more sensitive to tubocurarine. It is the *tibialis* of the cat which puts the drugs in the same order as does the hand-grip test in human volunteers. If the cat's *soleus* had been used, the relative potency of these drugs in the cat would have been different. By the same token, we do not know, as Drs. Paton and Zaimis have pointed out, how far the activities of these drugs in reducing the hand-grip in conscious volunteers correspond with their relative abilities to relax the abdominal muscles

of people under anæsthesia. I think we may agree with these authors that we can tell the relative action of different relaxants on such muscles only by observations made in clinical practice.

(*c*) *Release of histamine*.—The release of histamine is one of the most important side-effects we are likely to meet. How are we to detect and measure this release? At least two methods have been applied to muscle-relaxants in the laboratory. One is that of Rocha e Silva and Schild (1949), who were able to assay the histamine released when a solution of tubocurarine was shaken up with isolated rat's diaphragm.

Dr. Wien (Mushin *et al.*, 1949) used this method for estimating how far gallamine releases histamine. He concluded that it releases one-fifth to one-half as much histamine as does tubocurarine. If this figure were applicable to man, we might expect equipotent doses of the two relaxants to release about the same amount of histamine, since the synthetic compound has about one-fifth of the activity of the curare derivative. Various authors have reported evidence of histamine release by tubocurarine in man, but I do not know to what extent gallamine may have the same effect.

An alternative method of studying histamine release has been devised by MacIntosh and Paton (1949). In the cat a small intravenous dose of a compound which releases histamine will produce a rapid fall in blood pressure which lasts a short time. This fall resembles that due to injection of a little histamine, except that it does not start till about 20–25 seconds after the injection. The delay is presumably caused by the actual process of release. A fall in blood pressure of this type may be seen after injections of *d*-tubocurarine.

Since curarizing drugs are also liable to lower the blood pressure by blocking sympathetic ganglia, it is necessary, before using this fall as an index of histamine release, to block autonomic ganglia with a suitable agent.

By using this test MacIntosh and Paton showed that many organic bases including tubocurarine, dimethyltubocurarine and, to a much less extent, dodecamethonium iodide, are liable to release histamine. Some of their results are expressed in Table II, together with some results obtained by Depierre (1947).

TABLE II.—COMPARISON OF HYPOTENSIVE AND PARALYSING DOSES OF MUSCLE-RELAXANTS IN CAT AND DOG. DOSES IN MICROGRAMS PER KILOGRAM, INTRAVENOUS

Relaxant	Cat		Dog		Ratio of hypotensive to paralysing dose
	Paralysing dose	Hypotensive dose*	Paralysing dose	Hypotensive dose	
Tubocurarine Chloride ..	300	600	200	1,000	2 (cat) 5 (dog)
Dimethyltubocurarine iodide	50	600	—	—	12
Gallamine triethiodide ..	—	—	1,000–2,000	50,000	25–50
Decamethonium iodide ..	30	> 4,000	—	—	> 133

* After ganglia blocked.

Obviously the delayed depressor response provides a means of comparing in the cat or dog the doses which block the nerve-muscle junction with those which release histamine. I must leave the anæsthetists to decide how far the results agree with those in man.

(*d*) *Sympathetic block*.—The method which has been successfully used for studying sympathetic block involves recording the tension of the nictitating membrane of the cat's eyelid in response to repeated electrical stimulation of the sympathetic in the neck. This stimulation reaches the membrane through relays of ganglion cells. If these are blocked the tension slackens.

It is obvious, in view of the liability of muscle-relaxants to block autonomic ganglia, that a test of this type ought to be included in the overhaul of new muscle-relaxants.

(*e*) *Parasympathetic block*.—For the same reason we ought to investigate in muscle-relaxants their ability to block parasympathetic ganglia. Jacob and Depierre (1950) have used the response of the dog's heart to stimulation of the vagus to study this type of ganglionic block. And they found that gallamine blocks the dog's vagus at much lower doses than it blocks sympathetic ganglia. This finding satisfactorily accounts for the ability of gallamine to quicken the heart-rate in man, recently described by Drs. Wylie and Doughty.

An alternative preparation for studying parasympathetic block is that of the guinea-pig or rabbit ileum. Feldberg and Lin (1949) have shown that tubocurarine abolishes the reflex response of the ileum to increase in internal pressure, and Paton and Zaimis (1949) have shown the same effect with compounds like C6. Feldberg (1951) has also shown the ability

of tubocurarine and C6 to reduce the response of the ileum to nicotine. This preparation may therefore be used for study of parasympathetic block.

(2) *Effect on Respiration*

Can we foresee from experiments in animals how far a muscle-relaxant is likely to spare respiration in man?

TABLE III.—SPARING OF RESPIRATION BY MUSCLE-RELAXANTS. IN ANIMALS, VALUES ARE RATIOS OF DOSE ARRESTING RESPIRATION TO DOSE EFFECTING PARALYSIS. IN MAN, VALUES GIVE PER CENT OF NORMAL VITAL CAPACITY AT DOSES EQUALLY ACTIVE ON HAND GRIP.

(The figures in brackets give the order in which the drugs spare respiration)

Relaxant	Mouse	Rat	Rabbit	Cat	Monkey	Man
Tubocurarine chloride ..	2·5	1·8	1·5 (3)	1·7	1·5	69 (3)
Dimethyltubocurarine iodide ..	1·7	3·1	3·0 (1)	—	—	84 (1)
Gallamine triethiodide ..	—	—	1·7 (2)	1·9	—	80 (2)
Decamethonium iodide ..	1·2	1·2	1·0 (4)	2·45	2·6	39 (4)

In Table III I have put together comparisons of the dose which causes a certain degree of motor paralysis with that arresting respiration in various animals. In the rabbit, for instance, the ED50 or the head-drop dose is compared with the LD50. In the cat the reduction of *gastrocnemius* twitch is measured against reduction of respiratory volume. These figures are derived from the following authors: Collier *et al.*, 1948; Mushin *et al.*, 1949; Paton and Zaimis, 1948; Unna *et al.*, 1950*a*, *b*. Table II shows the same puzzling reversals in different species. There is no doubt that decamethonium spares respiration in the cat. It is equally clear that dimethyltubocurarine spares respiration better than decamethonium in the rabbit. The figures for man are those of Unna *et al.*, who compare effects on hand-grip and vital capacity. In this comparison man and the rabbit put the drugs in the same order; and so the rabbit happens to give a surer guide than the cat.

(3) *Duration of Action*

At equipotent doses, each muscle-relaxant has its own characteristic duration of action. Can we foresee from experiments in animals what the duration of action in man is likely to be? The usual difficulties apply.

TABLE IV.—DURATIONS OF ACTION OF EQUIPOTENT DOSES OF MUSCLE-RELAXANTS IN VARIOUS SPECIES IN RELATION TO TUBOCURARINE (= 100)

Relaxant	Mouse	Rat	Rabbit	Cat	Monkey	Man
Tubocurarine chloride ..	100	100	100	100	100	100
Dimethyltubocurarine iodide	100	1,100	200–300	>100	—	83
Gallamine triethiodide ..	—	—	—	67	—	70
Decamethonium iodide ..	—	—	—	<100	200–300	79

In Table IV I have collected data on the duration of equipotent doses of our four muscle-relaxants in various mammals. It is as puzzling as the others. Decamethonium iodide is longer than tubocurarine in the monkey, shorter in the cat (Paton and Zaimis, 1948). Dimethyltubocurarine is much longer than tubocurarine in the rat and longer in the rabbit and cat (*see* Collier *et al.*, 1948; Swanson *et al.*, 1949), but shorter in man. It is clear that each species has its own reaction to each muscle-relaxant and none of the animals in Table IV foreshadows correctly the order of duration of these four compounds in man.

(4) *Antagonism*

Any method of assaying muscle-relaxant activity in the whole animal appears to provide a means of estimating antagonism by other compounds. The LD50, the ED50 for loss of righting reflex or falling off a drum, the head-drop dose, the response of *tibialis* in the chloralosed cat and so on can readily be used (*see* e.g. Chase *et al.*, 1947).

If we are content to envisage neostigmine as an antagonist, then tests of antagonism need only use this substance.

A further question that arises is—how far is the antagonist liable to have unwanted side-effects? But I must leave both this and the question of developing new antagonists.

(5) *Administration with Anæsthetics*

The mouse loses its righting reflex after suitable doses of anæsthetics as well as of muscle-relaxants. By estimating the ED50 for loss of the righting reflex in the mouse after giving an anæsthetic and a muscle-relaxant separately and together, the relationship of the two drugs may be studied.

THE DEVELOPMENT OF NEW MUSCLE-RELAXANTS

From the foregoing I think it is clear that, while we must carry out in the laboratory tests of the types I have outlined, we must be exceedingly cautious in applying the results

to man. We must bear in mind the general rules of specificity, which may be stated thus: *Each chemical species has its own characteristic effects in living organisms; and each biological species has its own characteristic reactions to a chemical species. Specific differences may be quantitative or qualitative.*

The development of new muscle-relaxants is a process of approximation. First, we must assess the salient features of molecular structure likely to lead to muscle-relaxant properties. Then we must design compounds of a suitable type, make them, and assess their properties. It will then no doubt be necessary to modify the compounds in order to improve these properties. As this is a long task it must be done with fairly rapid biological tests. When compounds of high activity have been produced they must be carefully examined by the series of tests I have already described.

Molecular form and neuromuscular block.—To begin with—what molecular forms are likely to possess powerful muscle-relaxant action? This is such a wide question that I must immediately narrow it down to—what molecular forms are likely to oppose acetylcholine in a reversible way at the nerve-muscle junction?

Applying the well-established principle that substances of similar molecular form may oppose one another, we can see from the formula of acetylcholine that substances possessing quaternary nitrogen atoms may well antagonize it. This is a fact established many years ago by Crum Brown and Fraser, long before the advent of the acetylcholine theory of nerve-muscle transmission.

If we imagine that, on muscle fibres, and on other structures sensitive to acetylcholine, there exist receptors which take up this compound, then we may suppose that antagonists of acetylcholine might temporarily occupy these receptors at the expense of the natural compound. We might expect that a molecule with two quaternary nitrogens, provided their distance apart corresponds with the distance apart of the receptors, would adhere more strongly to the receptors than a molecule with one quaternary nitrogen. And, generally speaking, it is true that the blocking activity of a compound is increased by addition of a second quaternary nitrogen.

I have mentioned the distance apart of our imagined receptors. If this is regular, then we may expect an optimum distance for our quaternary nitrogen atoms. Such an optimum exists and, in fact, is now known to be round about the distance occupied by 10 carbon atoms in a methylene chain. It is well known then that quaternary nitrogen atoms placed at a distance of 10 carbon atoms apart, as in decamethonium iodide, are likely to have strong neuromuscular blocking activities. These considerations apply to blocking agents both of curare and C10 type. But while curare appears merely to block the access of the acetylcholine to the receptors, decamethonium carries the process a stage further, fires off the contraction process and depolarizes the end-plate for some time. Acetylcholine and hence neostigmine therefore, while antagonizing curare, tend to potentiate decamethonium (*see* Paton and Zaimis, 1949, 1950).

The fact that decamethonium iodide is not antagonized by neostigmine, owing to its mode of action, is a disadvantage of this otherwise excellent compound. The question arises—how can we produce molecules having equivalent potency to decamethonium iodide, but antagonized by neostigmine?

I should like to illustrate from work in our laboratories (Collier and Taylor, 1949; Taylor and Collier, 1950, 1951) one of the ways in which this problem may be tackled. In tubocurarine and its dimethyl ether the quaternary nitrogen atoms are placed in *iso*-quinoline rings, linked together by two chains (*see* Fig. 2 (*a*)). In decamethonium salts (Fig. 2 (*b*) the quaternary nitrogens are linked by a simple decamethylene chain. In our attempt to solve the problem posed above, Taylor prepared compounds in which

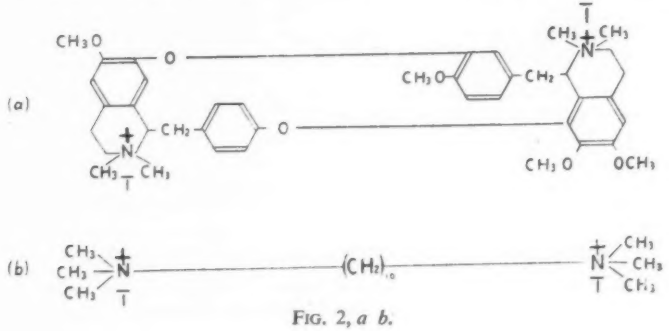

FIG. 2, *a b*.

quaternary nitrogen atoms, placed in *iso*quinoline, quinoline or other heterocyclic rings, were linked together by a decamethylene chain attached to the two nitrogens (Taylor, 1951).

The first compounds of this series he prepared—decamethylene-*bis*-quinolinium iodide and the corresponding *iso*quinoline derivative—both showed some ability to paralyse mice and rabbits. By a series of modifications of these compounds it was possible to produce substances of very high paralysant activity. Increase in activity was brought about by modifying the compounds in two directions: (1) by reduction of the heterocyclic rings; and (2) by introducing methoxy groups in the 6, 7 and/or 8 positions.

By reducing the quinoline compound to the 1.2.3.4-tetrahydroquinoline derivative, activity in the rabbit is increased about sixfold. Further reduction of the tetrahydro derivative to the *cis* or *trans* decahydroquinoline compound increased activity in the rabbit by about a further seven times. It is interesting that there is no appreciable difference between the activities of the *cis* and *trans* forms.

Similar results were obtained with the *iso*quinoline compounds. Reduction of the parent compound to the 1.2.3.4-tetrahydro derivative trebled paralysant activity in the rabbit. Taking the process of reduction further, the *cis* decahydro*iso*quinoline derivative was more than three times as active as the tetrahydro compound.

The second method by which we increased activity was by introducing methoxy groups in the 6, 7 and/or 8 positions. Introducing a methoxy group in the 6 position on the 1.2.3.4-tetrahydro*iso*quinoline compound increased activity in the rabbit about sevenfold. The 6.7-dimethoxy compound (No. 14, Fig. 2 (*c*)) and 6.7.8-trimethoxy derivative (No. 15, Fig. 2 (*d*)) were still more active.

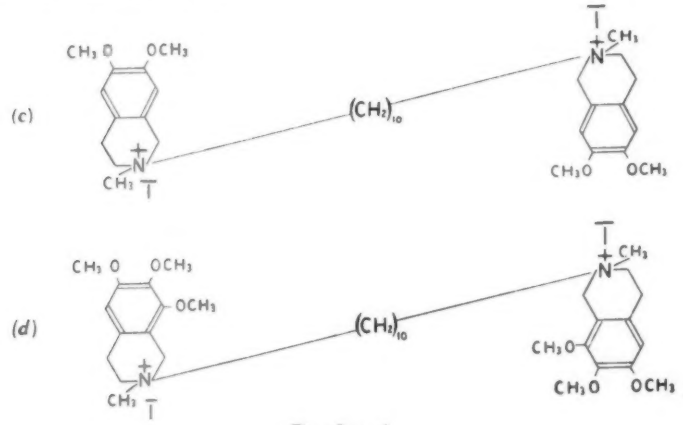

FIG. 2, *c*, *d*.

It will be seen from Fig. 2, in which the most active compounds are illustrated, that the process was one of making the end-groups resemble those of dimethyltubocurarine more closely. We have carried this process still further in Compound 20 (Fig. 2 (*e*)). It will be

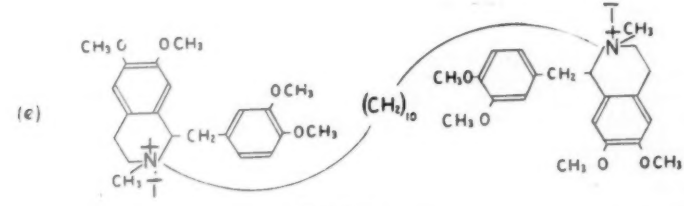

FIG. 2, *e*.

FIG. 2.—Synthetic compounds related to dimethyltubocurarine and decamethonium. (*a*) Dimethyltubocurarine iodide. (*b*) Decamethonium iodide. (*c*) Decamethylene-*aω-bis* [6.7-dimethoxy-1.2.3.4-tetrahydro*iso*quinolinium methiodide] (Compound 14). (*d*) Decamethylene-*aω-bis* [6.7.8-trimethoxy-1.2.3.4-tetrahydro*iso*quinolinium methiodide] (Compound 15). (*e*) Decamethylene-*aω-bis* [1.(3′ 4′-dimethoxybenzyl)-6.7-dimethoxy-1.2.3.4-tetrahydro*iso*quinolinium methiodide] (Compound 20).

seen that the end-groups of this compound resemble those of dimethyltubocurarine very closely indeed. In the cat, Compound 20 is the most active of all the synthetic compounds of this series that we have tried.

As might be expected, all of the compounds of this series which have been examined for this property are antagonized by neostigmine.

The development of compounds of this type raises further problems. Some of these problems arise because these compounds may antagonize acetylcholine not only at the nerve-muscle junction, but also in autonomic ganglia, or in relation to the enzyme which destroys acetylcholine. In short, these compounds may have ganglionic blocking or anti-cholinesterase activity. The latter type of activity has been demonstrated, for example, in polymethylene compounds bearing quaternary nitrogen atoms by Barlow and Ing (1948).

A second problem arises from the fact that many long chain organic bases, such as diamines and diamidines, liberate histamine, as MacIntosh and Paton have shown. In the diamines, liberation of histamine is greatest where there are 10 or 11 carbon atoms in the polymethylene chain.

We have attempted, in the case of the two most active compounds obtained—Numbers 15 and 20—to investigate a number of these questions in the laboratory by some of the methods described above. Some of the results of our work so far are summarized in Table V.

TABLE V.—PROPERTIES OF COMPOUNDS 15 AND 20 IN RELATION TO D-TUBOCURARINE (=100)

	Potency				Ratio LD50 to ED50	Dura-tion	Total hypo-tensive activity	Antag-onism neo-stigmine	Man	
Relaxant	Mouse	Rat	Rabbit	Cat	Rabbit	Cat	Cat		Potency	Hista-mine release†
Tubocurarine	100	100	100	100	100	100	100	+	100	100
Compound 15	23	5	600	*circa* 133	*circa* 120	*circa* 50	30	+	37*	200–1,200
Compound 20	23	4	360	„ 260	„ 90	„ 150	12	+	—	15–60

*Figure obtained by Dr. R. I. Bodman and colleagues.
†Ranges obtained by skin tests in two volunteers.

It will be seen from this table that both compounds are more active in the cat and rabbit and less active in the mouse and rat than tubocurarine. Compound 15 spares respiration in the rabbit more and Compound 20 less than tubocurarine. In the cat a dose of Compound 15 lasts about half as long as an equipotent dose of tubocurarine. On the other hand, the duration of action of Compound 20 in this animal is 50% longer than that of tubocurarine.

We have administered Compound 15 to a group of rabbits daily on five successive days without obtaining evidence of alterations in the animals' sensitiveness to the drug. We have also administered this compound to mice together with thiopentone or ether. As with tubocurarine and dimethyltubocurarine, the action of Compound 15 on the righting reflex is potentiated by ether. Thiopentone, on the other hand, has no obvious effect on the response of mice to Compound 15, as measured by loss of the righting reflex.

When Compound 15 is administered intravenously to the cat it lowers the blood pressure temporarily, after a short latent period. This depression is smaller than that produced by an equal dose of tubocurarine. Compound 20 also exhibits depressor activity in the cat, but it is less active in this respect than Compound 15.

My colleague, Miss B. M. Macauley, has investigated the release of histamine by Compounds 15 and 20, using the technique of Rocha e Silva and Schild. By exposing excised rats' diaphragms to 0·05% solutions of the drugs for thirty minutes, she finds that Compounds 15 and 20 liberate about the same amount of histamine as tubocurarine. Owing to certain technical limitations, however, the method does not appear to discriminate well with these compounds.

Dr. Bodman and his colleagues (1951) have administered Compound 15 to volunteers. They find that it possesses about one-third of the activity of tubocurarine in man. It thus shows the cat to be an unreliable guide to curarizing activity in man. The main side-effect of Compound 15, which appears to be the liberation of histamine, is important. At the dose giving 57% reduction of handgrip power (260 μg. per kg.) Dr. Bodman found side-effects, such as flushing, "pins and needles" and subsequent frontal headache to be severe. He confirmed this conclusion by injecting Compound 15 intradermally, when a marked wheal and flare similar to that given by histamine was produced. Considerably lower doses of Compound 15 than of tubocurarine were required to produce this response.

In view of Dr. Bodman's findings, and since Professor Bain (1949) has shown that the areas of wheals produced by intradermal injection of histamine in man bear a linear relation to the logarithm of the dose, we have attempted to compare the histamine-releasing potencies in man of Compounds 15 and 20 with that of tubocurarine by intradermal injection of graded doses in two volunteers. The results, which are expressed in Table V, confirm Dr. Bodman's conclusion regarding Compound 15, and indicate that Compound 20, on the other hand, is considerably less active than tubocurarine in this test.

Compound 20 has not yet been administered to man except in skin tests. In view of the difficulties I have described in the interpretation of animal experiments, I will not permit myself any forecasts of its possible activity or side-effects.

ACKNOWLEDGMENTS

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Dr. R. I. Bodman: The results of clinical trials of "Compound 15 (A & H)" carried out by us in conscious volunteers may be seen in the Table I. Nine trials were done with doses varying from 1 to 20 mg. In each case the drug was injected into a volunteer whose hand-grip power and maximum inspiration were measured at intervals of two minutes. Significant reduction of power was seen only in the ninth case, in which over 50% reduction was brought about by a dose of 0·26 mg. per kg. body-weight of "Compound 15": an equivalent reduction might be expected from a dose of about 0·50 mg. per kg. of gallamine triethiodide ("Flaxedil"). In other words "Compound 15" has a potency about twice that of gallamine. Its duration of action is of the order of half that of gallamine.

The side-effects, which varied in severity from case to case, were "pins and needles", with flushing of the face and upper part of the body, accompanied by palpitations and tachycardia; these were followed by a frontal headache. The character of these effects and their successive onset led us to believe they were due to release of histamine; they became so severe that we decided it would be unwise to proceed with experiments on volunteers and unjustifiable to give the drug to anæsthetized patients.

TABLE I

RESULTS OF CLINICAL TRIAL OF "COMPOUND 15" IN CONSCIOUS VOLUNTEERS

Subject					Response			Side-effects			
No.	Volunteer	Wt. (kg.)	Dose (mg.)	Dose/wt. (μg./kg.)	Double vision	Reduction in hand grip	Reduction in max. inspn.	Pins and needles	Flushing	Palpitations	Headache
1	A	77	1	13	0	0	0	0	0	0	0
2	B	64	2	32	?	0	0	0	0	0	0
3	C	74	4	54	?	0	0	+	+	0	0
4	D	72	6	83	+	0	0	++	++	+	++
5	A	77	8	104	+	0	0	+	+	0	0
6	E	89	10	112	+	0	0	0	0	0	0
7	E	89	14	157	+	0	0	0	0	0	0
8	F	68	12	175	+	0	0	+++	+++	+	0
9	A	77	20	260	+	57%	0	+++	+++	+++	+++

Dr. Ronald Woolmer asked what reactions, other than hypotension, were used as evidence of histamine release, since hypotension itself might be attributable to a ganglionic blocking effect. Secondly, it was known that adrenaline acted to some extent as an antagonist to the depolarizing muscle relaxants, and he thought that the possibility of a high blood adrenaline in conscious volunteers should be taken into account, if the drugs to be tested were also affected by adrenaline.

Dr. A. H. Galley said that he noted that Dr. Collier discarded synthetic muscle relaxants which reduced blood pressure by means of histamine release ("histamine flush"). He wondered, however, whether it were possible to build up molecules containing one pair of quaternary groups separated by a ten carbon atom chain and another pair separated by a chain of only five (or six) carbons, thus:

$$\begin{array}{l} CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.N.(CH_3)_3.I \quad \alpha \\ \quad | \\ CH_2.CH_2.CH_2.N.(CH_3)_3.I \quad \beta \\ \quad | \\ CH_2.CH_2.N.(CH_3)_3.I \quad \gamma \end{array}$$

Hypothetical molecule containing three quaternary ammonium groups (α, β and γ) in which β and γ are separated from α by a chain of ten carbon atoms, whilst they are separated from each other by a chain of only five carbon atoms

Such a substance (assuming that some molecules did not neutralize the curarizing effect of others) might make it possible to obtain muscular relaxation and a bloodless surgical field (paralysis of sympathetic ganglia) with one and the same injection.

Dr. Collier (in reply): It is useful to have Dr. Bodman's results before us in detail to remind us how far we succeeded and how far we failed in foretelling human reactions to Compound 15 from animal experiments. We correctly inferred that in man Compound 15 would prove to be a muscle-relaxant of high potency and of short duration of action, which might release some histamine. We were incorrect however in thinking, from experiments in the cat and rabbit, that Compound 15 would be more active than tubocurarine in man and that full relaxant activity would be manifested by doses which did not release histamine.

As Dr. Woolmer says, it is necessary to block sympathetic ganglia in the cat before estimating release of histamine. But, without blocking ganglia, if a dose of drug causes no fall in blood pressure, it seems reasonable to conclude that no histamine has been released. Tests have shown that in the cat, even after blocking the ganglia, Compound 15 has less hypotensive activity than tubocurarine. Since this is the reverse of the situation in man, I believe that the human skin test described above is a better test for our purpose.

I agree with Dr. Woolmer that adrenaline may interfere with results obtained with muscle-relaxants in volunteers.

In reply to Dr. Galley's interesting suggestion, I think it would be possible to make branched molecules on the principles he proposes; and it is certainly possible that the effects might be the expected ones.